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THE ABSOLUTE CURABILITY OF CANCER OF THE BREAST

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IN this article an attempt will be made to assess and measure the absolute curability of cancer of the breast. Most papers giving curability rates for this type of cancer use the 5 year survival rate as the standard of cure. The fallacies of this standard, as usually employed have been pointed out by Lees and Lees (1950); and it is, in any case, a comparative standard, comparing different degrees of curability, not a means of assessing the absolute curing ability of any treatment.

PART I.—DISCUSSION

There is no doubt that the more extensive a tumor of a given type at the date of treatment the worse the prognosis. This well-established fact is the background for the frequently made statement that "the earlier the treatment, the better the chance of cure." Without more definition, however, this statement does not distinguish the two meanings of the word "early"—early in the sense of less extensive, and early in the sense of shorter duration. This distinction is fundamental for the reason that "extension" at the time of treatment is, or may be, a function not only of (a) the duration since onset of symptoms, but also of (b) the growth rate or "intrinsic malignancy" of the tumor. This in turn points to the distinction that may be made between *real* and *apparent curability.*

Let us assume a series of cases of breast cancer divided into two groups: (a) those with axillary metastases present at the time of treatment and a 5 year survival rate of 20 per cent of such cases, and (b) those without axillary metastases at the time of treatment and a 5 year survival rate of 70 per cent.

The *real cure rate* in this series is represented by the difference between the 5 year survival rate of all the cases after treatment and what would have been the 5 year survival rate of those same cases if they had not been treated.

Now, if one could correctly assume, first, that all those cases if untreated would have had a nil per cent 5 year survival rate, and, second, that cases with axillary metastases differed from cases without axillary metastases only in delay in diagnosis (that is to say, those cases with metastases present at the time of treatment would also have had a 70 per cent survival rate if they had been diagnosed with the same average delay as those found in fact not to have metastases), the figures as they stand would be a correct index of the real cure rate. As it is, neither assumption is justifiable; so that figures such as these which are in fact based on those assumptions must be taken as indicating only an *apparent cure rate.*

The first assumption is of little significance in the actual calculation of a survival rate, though the implicit fallacy must be remem-

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bered in any appreciation of the curability of cancer in general. With regard to the second assumption the practical point is that if the amount of extension is dependent only upon the amount of delay in treatment, the apparent cure rate does express the real cure rate. If, however, extension depends more or less upon intrinsic malignancy, and not upon delay in treatment, the real cure rate is less than the apparent cure rate correspondingly more or less. That this is so can probably best be demonstrated diagrammatically.

In Figure 1 the size and extent of a tumor is measured along Oy, and the duration from onset of malignancy along Ox. If it is assumed that the tumor has a constant rate of growth this growth rate will be represented by the slope of the line OA. Let D be the least extent of the tumor at which it can be diagnosed in practice (presumably at the onset of symptoms); M the size and extent where there are regional but excisable metastases; C the limiting extent technically of complete tumor cell destruction or excision; and L the size and extent required to kill. By current concepts the cure rate in a series of cases will be the proportion of cases treated before the date c, during the time interval dc.

However, all biological phenomena have variability, and all our measurements of these have error. These variabilities, in respect of tumor growth, may be discussed as follows.

1. *Variations in the growth rate of individual tumors.* Taking the onset of malignancy as base, it is clear that some tumors will be diagnosed, metastasize, etc., earlier or later, at a greater or less extent, than the average durations or extents for the tumor type.

In Figure 2 the range of this variability has been represented by the space between the lines oA and o_1A'. The essential point here is an acceptance of the reasoning that although some tumors will be diagnosed earlier or later than the average these variations, whether by extent or by duration, will be random; and, therefore, there will not be a tendency for an individual tumor which is diagnosed at a shorter duration in the life of the tumor to metastasize sooner, become incurable sooner, or kill sooner, and vice versa. d is the average date of earliest possible diagnosis, and d_1 the date of actual diagnosis and treatment in a group of tumors with the same delay in treatment.

In Figure 3 the opposite reasoning is accepted, so far as the time factor is concerned. It is assumed that these variations are not completely random but that some individual tumors are more rapidly growing than others over their whole course; in other words, that tumors which kill sooner tend to be diagnosed sooner and spread quicker, and vice versa.

These diagrams represent two extremes, but it can be seen that with the conditions of Figure 3 it would be possible to have a very high apparent cure rate but a low real cure rate, for the reason that if the tumor type has a wide range of growth rates in individual tumors, only tumors with growth rates in a restricted part of the range will contribute to the real cure rate (zone Q in Fig. 3). Many tumors will be so rapidly growing that treatment is always hopeless (zone P). Many will be so slow growing that the patient would have survived for 5 years or not had her life shortened at all, even without treatment (zone R).

An overall true or real cure rate of 5 per cent represents a very much higher true cure rate in those tumors in the restricted part of the range amenable to effective treatment.

2. *Variations between the directions of spread.* In Figure 3 the lines DD', MM', CC', and LL' have been represented as straight lines and parallel with each other. This is to assume that "size," that is, the number of malignant cells, and "extension" mean the same. It is clear, however, that in the study of cancer a distinction must be made between *growth-rate*—the rate of reproduction of malignant cells—and *malignancy*—infiltrativeness and metastasizing potential. Certainly that holds between different tumor types, and probably also within a single tumor type. In other words, for a series of tumors of a given size, that is, of a given number of malignant cells, some tumors would have infiltrated and extended further than others. So little is known of the behavior of cancers in the human body that we can only surmize that these differences are not due entirely to chance but are systematically associated with

some factors—the growth rate of the tumor, its anatomical location, the age of the patient, her general state of health, and so on.

3. Variations in the date of onset of symptoms and limit of curability. It can be assumed that a tumor will have to achieve a certain size before it crosses the threshold of exciting symptoms; and this critical size will have its own variability in different patients. For want of better information it must be assumed that this variability is random. It is really probable that a more rapidly growing tumor will excite symptoms at a smaller size than a slow growing tumor, but within our knowledge the size will be random for tumors of the same growth rate. There will be similar random error in our estimate of when the tumor extension has crossed the line MM'. The actual calendar dates of treatment and of death will be known accurately; and the fact that the extension was beyond the line CC' at the date of treatment can be presumed if the tumor recurs outside the zone of excision.

4. *Variations in the relation of the individual tumor to the average.* Figure 2 has been drawn in such a form that a stream of dots, each representing an individual cancer, can be imagined as moving steadily upward between the lines oA and o_1A'. Leaving aside the question of temporary cessation, or even regression, of growth, each dot will move inexorably upward, though in a randomly zigzag way, unless and until it comes to the barrier of successful excision. The dots will tend to be concentrated in the middle of the stream, and in cross section of the stream will take some selective, more or less "normal" distribution. That applies to estimates of the distribution in cross section throughout the full length of the stream, but for diagrammatic purposes the number of tumors in any of the classes at any time or at any stage of extension, i.e. in any of the compartments along the length of the stream oA/o_1A', can be taken as equivalent to the area or length of the corresponding compartment.

If, for a series of cancers, the appropriate data were given—the survival time, the presence of removable metastases or inoperable metastases at the time of treatment and later, and the delay in treatment—the number of cases in each compartment would be known. The lines MM' and CC' and the scale of duration to extension could be drawn so that the area of each compartment would correspond to the number of cases in it.

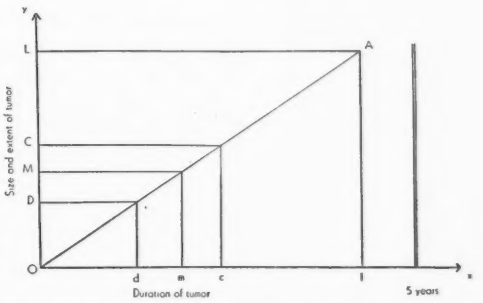

Fig. 1. Diagram showing the relation of tumor growth rate, size, and duration.

5. Variation in the relation of malignancy to incurability. In both figures 2 and 3 the line CC' has been put higher than the lines DD' and MM', that is, it has been assumed that there is an interval, both in extension and time, between the date when the tumor first becomes diagnosable and when it gives regional and, later incurable general metastases.

In some tumor types, and in some examples of nearly all tumor types, this interval—what may be called the "available time margin"—is so small that, in practice, such tumors are incurable even at the earliest practicable date of treatment. The very important question arises whether all tumors which have the ability to metastasize may not already have done so at a very early stage in the life of the tumor, in fact long before we could hope to diagnose the cancer and treat it. The delay in the manifestation of the mestastases could be explained in several plausible ways. If a metastasis is growing at the same rate as the primary tumor but with a lag in time equal to that required for either tumor to double itself in size five times, this would mean that a primary tumor starting from a single cell has metastasized (with a single cell) when it was 32 cells large. Moreover, the casual locations, varying growth rates, and long delay of some recurrences can be explained only by invoking local and general resistances to neo-

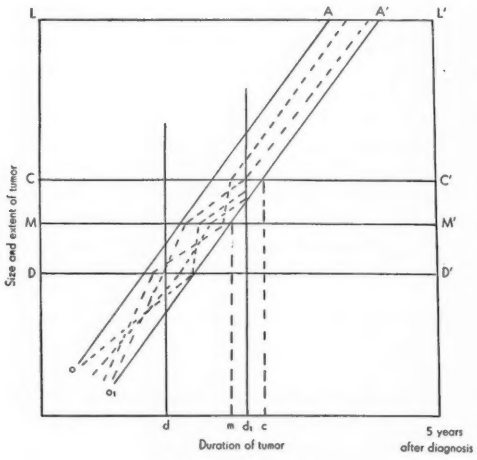

Fig. 2. See text.

plastic growth of which nothing is known except that they must exist and that they must vary in different tissues and at different times. If, therefore, it was found empirically that the end results of treatment could best be explained by the coincidence of the lines *CC'* and *DD'* there would be no theoretical objections to this as an explanation of incurability.

6. The error of small sampling. Estimates of any of the factors mentioned will, of course, approximate more closely to the "true" average values, the greater the number of cases that are measured.

Relationship between real cure rate and apparent cure rate. From Figures 1, 2, and 3 the following principles can be recognized:

1. Proof of curability will be given by a positive relation between decrease in survival rate and increased delay in treatment after onset of symptoms—for patients with cancers of the same degrees of malignancy.

2. The more rapidly growing the tumor, the less will be the duration between the extension at *M* and at *C* (i.e. in Figure 3 the less will be the time intervals *dm* and *dc*), the less the margin of time available for successful treatment, and the greater the diminution of survival rate for a given time delay, and vice versa. The interval *dc* is, again, the available time margin.

The relation decreased survival rate to increased delay in treatment will therefore vary with the available time margin which is, as we have seen, the less the more rapid the intrinsic growth rate or malignancy of the tumor.

There are two ways of estimating the intrinsic growth rate: (a) It can be estimated by the histological appearances of the tissue. In so far as the size or extension of the tumor at the time of diagnosis is allowed to intrude and give weight to the estimation, however, such histological grading will not be independent, and will not measure purely the intrinsic malignancy. (b) It can be estimated in terms of the duration of survival from date of treatment or onset of symptoms to death in untreated or unsuccessfully treated patients. It is possible, of course, that the survival time is affected by treatment even if unsuccessful. This will certainly be so for such tumors as cancer of the thyroid in which death can frequently be attributed to the direct effect of the primary growth itself. In cancer of the breast, however, the excisable parts of the cancer in the breast and axilla would have contributed little to the lethal mechanism even if they had not been removed. They might have increased the reservoir for further tumor emboli, but, if we accept the concept on which present cancer treatment is based, death is due to the growth of internal cancerous foci either already deposited at the time of treatment or derived from other foci already deposited elsewhere outside the zone of excision. Whether the growth rate of these foci is affected by removal of the primary growth is another matter of which nothing is known.

If in a series of cases the overall relation "decreased survival rate to increased delay in treatment" is regarded as the mean of the individual relations, the wider the variability of the individual relations the more difficult it will be (i.e. the more cases will be required) to define the overall relation, that is, to prove that treatment is effective.

3. If we assume, as before, a series of cases of breast cancer divided into two groups, those with axillary metastases present at the time of treatment and a 5 year survival rate of 30 per cent of such cases, and those with

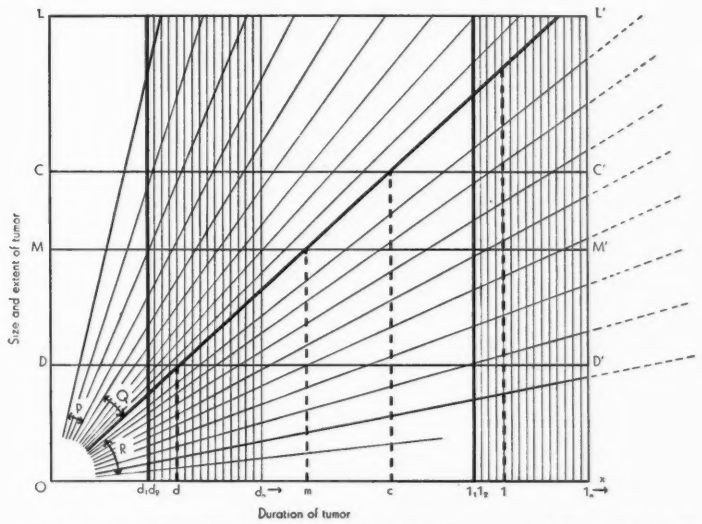

Fig. 3. See text. Each *d* line represents the date of earliest practical diagnosis for each tumor growth rate. The intervals d_1 to 1_1, *d* to 1, d_n to 1_n each represent 5 years, i.e. each 1 line lies 5 years after the corresponding *d* line. The more rapidly growing the tumor the earlier in time after onset of malignancy will be the date of earliest practical diagnosis, and the more to the left will be the vertical *d* line. *d*, *m c*, and 1 correspond for one representative tumor. Cancers of the breast may be so slow growing that they will not be diagnosed for many years after onset of malignancy; and they may not shorten the patient's life. For completeness, therefore, the *d* lines and 1 lines should have been drawn along the *x* axis to 2 or 3 times the width of this graph but for clarity they have been omitted to the right of d_n and 1_n. In practice the actual dates of diagnosis will occur at a varyingly later date than the earliest practical date of diagnosis. In so far as they occur later than *c* for each tumor growth rate the cancers will be uncured. The cure rate for each tumor growth rate will be given by the proportion of tumors diagnosed within the time interval *dc*, which will be the less the more rapid the growth rate.

no axillary metastases and a survival rate of 70 per cent: (a) From these data alone nothing can be said of the real cure rate except, of course, that it will not be greater than the apparent cure rate. (b) If the behavior of the tumor is that of Figure 2, the real cure rate is the same as the apparent cure rate. The line o_1A' might have overlapped the 5 year post-treatment duration line, and there would probably always have been some tumors which were incurable at the time of earliest diagnosis, but, on the average, the cure rate could be expected to increase or decrease as the zone of diagnosis was switched to the left or the right along the *x* axis. (c) If it is known from other evidence that the growth rate of the tumor is very variable, as in Figure 3, the real cure rate will be less than the apparent. If the tumor type is quite incurable, that is, if tumor growth and metastatic spread are quite unaffected by treatment, then the figures given for this series will reflect the variability of growth rate of different tumors treated or untreated.

The onus of proof. In order to investigate the absolute curability of cancer of the breast, it is necessary to start with the null hypothesis that cancer is incurable until it is proved to be curable; and the difficulties of this proof are great.

The evidence to be examined will lie in the records of one or more series of patients with breast cancer. In each series, the cancers will have been diagnosed by one or more surgeons in one or more hospitals, the cancers therefore having been contributed to the

series by all manner of routes selectively weighted in unknown ways by degree of malignancy, social class of the patient, urbanization, local custom, the professional reputation of the surgeon and so on. The threshold of diagnosis has an appreciable variability and since in most series the data refer only to patients subjected to operative treatment (with or without radiotherapy in addition) there will be also the differences in standards of operability. All series extending over many years will have changing standards over the decades. Even at this stage, then, the data about this variable disease will be more or less suspect.

Next, the proportion of survivors 5 years after treatment must be found. Having found this, we have then to discover from the internal evidence of the data themselves what the 5 year survival rate would have been if a series of cancers containing the same proportions of the different grades of malignancy had not been treated. Having found this value, we then compare the treated and untreated survival rates. The standard error of the difference between two proportions each about 30 per cent and with 100 cases in each is roughly 6 per cent so that, even though there were no difference in the survival rates due to treatment, one could expect a difference due to chance alone up to the order of 12 per cent over a large number of such comparisons. This comparison between the survival rates of treated and untreated cases cannot be made directly because the information about untreated cases is never available for obvious reasons; but whatever the indirect method used and however accurate and unbiased the data, if the standard of curability is taken to be the 5 year survival rate the inescapable variability due to the smallness of the sampling must always be present.

It will be seen that proof that treatment is effective at all will be very difficult to obtain. Such "proof" will at best carry an unanalyzable residuum of doubt whether the evidence used may not be biased and unreliable in an unknown way; and the possible bias itself may be of a degree which will seriously affect the validity of curability rates of the order, we suggest, of 10 to 15 per cent. By statistical methods one may define the probability of the null hypothesis being true—if the errors in the data are random. But this uncertainty, mathematically defined though it may be, is no better than ignorance if there is no means of knowing how much selective bias there is in the data and in the collection and measurement of the data.

The variability in growth rates of cancers of the breast. The great range of variability of behavior in diagnosed cancer of the breast raises acutely the question whether there may not be a continuous gradation of cancerousness from tumors diagnosed as noncancerous to tumors diagnosed as cancerous. It may reasonably be argued that there is indeed such a gradation.

It is very rare for a breast tumor identified by a competent pathologist as nonmalignant to metastasize subsequently and prove him wrong in his prognosis. The converse, that his prognosis should always be right when he identifies a tumor as malignant, is scarcely credible. It may be that there are laboratory tests, say for the presence or absence of a given bacterium, which will allow accurate prediction of the behavior of the complicated human organism over the subsequent 5 years, and there may be some tumor types, such as bronchogenic carcinoma, in which, if given sufficient tissue, accurate prediction is possible. In cancer of the breast, however, one has to worry so often whether to call a tumor malignant or not; there is so much difference between opinions on borderline cases; and so much of the "probably not cancer but safer away" type of diagnosis, that there can be no doubt that many tumors treated as if they were malignant were, in fact, not malignant at all.

It does not necessarily follow of course, that the factor which leads to this doubt in diagnosis, namely, the gradation in the clinical and histological manifestations of the tumor, is correlated with a similar gradation in the growth rate of the tumor or in its rate of subsequent extension, that is its "malignancy," if it should later prove to be metastatically malignant. Some of the difficulties in diagnosis are no doubt due simply to the earliness of the date of diagnosis in that the man-

ifestations have not had time to become fully developed, difficulties which would be present whether the tumor were subsequently of great or of little malignancy. Nevertheless, the factors which characterize malignancy under the microscope and by which cancer is microscopically diagnosed, namely, *growth rate* as shown by cell polymorphism, mitotic frequency, etc., and *extension* as shown by undue infiltration, etc., are the same characteristics as those which, on a macroscopic scale, comprise the state of cancerousness and which, within the limits of our present knowledge, make cancer "cancer" and a lethal disease. It is reasonable to infer, therefore, that when the microscopical diagnosis is in doubt this is, to some extent at least, due to the fact that the tumor is so slow growing and so little cancerous that it is in the borderline zone of a gradation from "nonmalignancy" to "malignancy."

Clearly any discussion of cancer in terms of degree of malignancy at the lower border of malignancy requires definition of what is meant by "malignancy." The concept is being used here in the composite sense that a tumor of great malignancy has a rapid rate of increase of size, early and frequent metastases and a short survival time; and tumors of low malignancy the opposite of these. A definitive borderline would be drawn between those tumors which, if untreated, shorten the life of the patient and those which do not.

Pragmatically diagnosed cancer. It will be necessary, then, to distinguish between real cancer—which, if untreated, will kill, and pragmatically diagnosed cancer—cancer so called because at the time of diagnosis, for practical reasons, we can do no other. For all lesions called operable cancer the treatment is fundamentally the same. Much less justifiably, current methods of assessing the effect of treatment use an arbitrary standard, the presence or absence of 5 year survival, which makes no attempt to measure the degree of either cancerousness of the lesion or of effectiveness of treatment. In practical treatment of the individual patient there is no alternative to pragmatically diagnosed cancer; but in trying to assess the curability of cancer we must think in terms of real cancer. The fallacy that underlies nearly all our notions of the curability of cancers is that this distinction is not made.

The maximum expectation of curability. Approximately 20 to 40 per cent of all patients with cancer of the breast treated or untreated are stated to survive for 5 years after diagnosis, and of patients untreated for various reasons, of which, no doubt, the main reason was that they were untreatable, 10 to 22 per cent survive for 5 years. Any increase in 5 year survival due to treatment, therefore, cannot be more than 25 per cent. Further, since there are undoubtedly great differences in the growth rates of different cancers of the breast, and since the more slowly growing tumors will certainly have a better chance of being considered operable and of allowing 5 year survival than the fast growing tumors, the true and theoretically possible 5 year survival must be considerably less than 25 per cent.

The maximum expectation of curability can be approached in another way.

Our figures given later show that of patients with diagnosed cancer of the breast 60 per cent have discoverable axillary metastases at the time of onset of symptoms, and that of patients in whom treatment has been delayed for 3 years 75 per cent have such metastases. Let us assume that patients with axillary metastases at the time of treatment have a 5 year survival of 20 per cent and those without of 70 per cent.

The overall survival rate of those treated at the onset of symptoms will then be

$$\frac{60\times 20+40\times 70}{100}=40.0 \text{ per cent.}$$

The overall survival rate of those treated 3 years after the onset of symptoms will be

$$\frac{75\times 20+25\times 70}{100}=32.5 \text{ per cent.}$$

The difference in the survival rates in the two groups of patients will be 7.5 per cent. This will be the maximum expectation of curability, accepting these figures which are in accord with general experience.

There are two possible explanations for the fact that the proportion of patients with

axillary metastases increases with delay in treatment:

1. The first is that malignant cells left the primary tumor for the axillary lymph nodes during the period of delay. If the primary tumors had all been excised at the date of onset of symptoms, the incidence of axillary metastases in women examined 3 years after the onset of symptoms would have been 60 instead of the 75 per cent actually found.

2. The second explanation is that malignant cells left the primary tumor for the lymph nodes long before the onset of symptoms. In 60 per cent of the patients the metastases were discoverable at the time of onset of symptoms. In another 15 per cent of all the patients it required up to 3 years further growth of the malignant cells for the metastases to be demonstrable. Even if the primary tumor had been removed in all the patients at the date of onset of the symptoms the incidence of axillary metastases 3 years after would still have been 75 per cent. The rate of appearance of demonstrable axillary metastases will be no more than a manifestation of the variation in rates of tumor growth and spread. It will be unaffected by removal of the primary tumor.

One method, the direct method, of finding which is the correct explanation would be to remove the primary tumor in some of the patients at the date of onset of symptoms and show that the incidence of axillary metastases 3 years later in these patients was, or was not, less than in the remaining patients whose primary tumors had been left *in situ* for the 3 years.

Another method, the indirect method, would be to measure the growth rate of the tumors independently of their extension. If it could be shown that the fact and time of appearance of axillary metastases ran exactly parallel to the growth rate, i.e. was completely determined by the growth rate, we could say that the amount of delay in removing the primary tumor had no influence on the incidence of axillary metastases and that the second explanation was the correct one.

In practice there is no information available for the direct method although there is for the indirect.

The real interest, of course, is not in the relation between removal of the primary tumor and the incidence of axillary metastases but in the step further on, namely, the relation between removal of the tissue at radical mastectomy and the incidence of distant lethal metastases. The same principles apply with the same two types of possible explanation.

It is the purpose of this study to gather and assess the relevant information in order to discover which explanation is correct.

We will anticipate the findings by saying that all the evidence points to the second as the correct explanation: in other words, that radical mastectomy has no influence in diminishing the incidence of distant metastases nor in preventing or postponing death from the growth of such distant metastases.

THE SCHEME OF STUDY OF THE ABSOLUTE CURABILITY OF CANCER OF THE BREAST

We can attempt to find the absolute curability of cancer of the breast in two ways. (a) By showing that the curability decreases as the delay in treatment increases. This will define the positive limits of curability. (b) By finding how far the index of effective treatment—survival time or survival rate—is a function of the individual tumor growth rates. The more closely the survival time or rate can be explained in terms of the growth rate determined in some other way, the less will be the margin available for true curability.

This will define the limit of curability negatively, since, if a close relation between survival rate and growth rate is not found, this may be due not only to the influence of delay in treatment but also to the inadequacy of our measurement of the growth rate.

If this cannot be recognized intuitively by study of Figures 2 and 3, there is probably no other method of giving conviction. Both these methods will be used and the scheme to be followed will be:

Part II. Relevant quotations from the literature will be given on the relation between delay in treatment and diminution in survival rate. This comes under (a) above.

Part III. Data of our own relating the incidence of axillary metastases to delay in treatment will be given. Since the presence

of these metastases is assessed from tissue removed at radical mastectomy (i.e. contemporaneous with removal of the primary growth) the relation found will do nothing to prove which of the two explanations is correct. It will, however, give some idea of the time factors involved and set upper limits for the behavior to be explained by either method (a) or method (b).

Part IV. A set of published figures will be analyzed in the hope of relating survival time and survival rate to the tumor growth rate determined in other ways. This comes under (b) above.

PART II.—THE RELATION BETWEEN DELAY IN DIAGNOSIS AND THE 5 YEAR SURVIVAL RATE

Cancer of the breast has many advantages as a type tumor for assessing numerically any relation which may exist between the delay in treatment and a diminution in curability. It occurs frequently; although it is sometimes preceded by a nonmalignant mastopathia, the date when the cancer was first noted is usually accurately known; it is relatively chronic in its course, and, as a surface tumor, the stages of its extension can be fairly well demarcated clinically; it is semicurable or, at any rate, has a significant 5 year survival rate; the average delay between onset of symptoms and treatment is about 12 months. It is as well adapted as any tumor type for defining the relation between delay in diagnosis and survival rate.

We cannot pretend to have read any but a small part of the enormous literature dealing with cancer of the breast but the following is a summary of all the references concerning this relation which we have found in our reading. We can remark, however, on the paucity of references to this fundamental relation, and, with still more surprise, on the absence of interest in the matter when the relation has been noted to be absent or small. If there is no empirical confirmation that "delay in treatment lowers the curability" most of cancer treatment loses its rationale.

"Buchanan pointed out that in 70 cases in which operation was done from one to thirteen years after the onset of cancer the incidence of cure was 11 per cent higher than in 153 cases operated on within the first year of the disease" [quoted by Taylor (1932, p. 9)].

Daland (1927) described the survival times in 100 patients with cancer of the breast who did not have treatment. It was recorded in 23 of the patients' notes that operation was refused and in 23 that the tumors were inoperable when first seen. In 3 the general condition did not warrant operation.

"The average duration of life from the time of the first symptom to death was 40.5 months.

"In those patients in whom the cancer was detected early and in whom operation was advised the average duration of life was 42.8 months.

"Those in whom the condition was inoperable at the first examination lived 29 months."

The median duration was 29 months. A study of the degree of malignancy, as made by microscopic study failed to show any relationship between the length of life and the degree of malignancy.

Davis (1920) recorded 166 cases in which patients were operated on from 1898 to 1916. He remarked (p. 271):

"The time the growth was first noted is given in almost all the histories. The average time between the discovery of the 'lump' and the day of operation in those operated before 1910 was one year, three months, eight days, while those operated during the years 1910 to 1916 were aware of the growth one year, five months, eight days before the operation, a difference in favor of the earlier group of exactly two months. A partial explanation of this apparent lack of progress is that in the 1910 to 1916 period are included two women with tumors of thirty and fourteen years' standing, respectively.

. . .

"Statistics are peculiar things. It is also found that the average time between the discovery of the 'lump' and the operation of those that died of recurrence is practically the same as of those that have remained free of the disease. These apparently contradictory figures should not lessen our determination to operate as early as possible in every case."

Eggers, de Cholnoky, and Jessup (1941) gave some interesting figures in their account of 505 patients. In their Table II they showed that 54.9 per cent of the patients come to consultation within 1 year of the onset of symptoms, 14.4 per cent between 1 and 2 years, 7.2 per cent between 2 and 3 years, and 7.9 per cent after 3 years. (In 15.5 per cent, the duration was not stated.) In their Table IV

they related the size of the tumor to the incidence of axillary metastases. The gist of the relation is given by extracting the percentage incidences with tumors of 1, 4, and 10 centimeters. These are 25, 68.5, and 100 per cent respectively.

The relation between delay in treatment and survival rate was given in a table illustrated in a diagram and can be summarized by quoting the legend to their Chart 1:

"Illustrating the percentage of five-year arrest cases in relation to operative delay: there is a gradual reduction in five-year arrests in cases in which operation was delayed from one month (76 per cent) up to two years (20 per cent). After that, there is a definite increase in recoveries.

"The probable explanation is that the more malignant cases die during the first two years after recognition of the tumor. Those who survive probably represent so-called favorable tumors from a malignancy standpoint. Either the cells in themselves, are less malignant or the resistance of the host is greater than usual."

Their Table VII related the size of tumor at treatment with the 5 year arrest. Their summary of these figures was that when the tumor is ½ to 2, 3 to 6, and 6+ centimeters, the 5 year survival rates are 72.5, 24.4, and 15.5 per cent, respectively.

We can also quote (p. 333) the following as epitomizing the present status, not only of the treatment of cancer of the breast but of the study of the treatment.

"Willy Meyer's report, in 1905, which includes all his cases since he proposed the radical operation in 1894, and presents 30 per cent five-year results obtained in unselected cases, is as good as those reported from most clinics to-day, even with the addition of postoperative radiation.

"White's communications, in 1927 and 1937, are interesting as showing that in spite of becoming more radical in his operative procedure and adding postoperative radiation, his statistics, in 1937, are well below those of 1927. As he himself states, this may be due to more accurate pathologic reports and a better follow-up. Perhaps uniform criteria of operability will aid in comparing statistics."

Finney, Merkel, and Miller (1947) gave a table (Table V) from which it appeared that 211 of their patients allowed 6 months or less to elapse after discovery of the tumor and before treatment; and 31, 24, 9, 2, 10, and 5 patients had delays of 1, 2, 3, 4, 5 to 10, and 15 to 20 years, respectively. In this series, the survival rates were 77, 49, 19, and 4 per cent at the end of 3, 5, 10, and 15 years, respectively.

There can be no doubt that cancer of the breast is a very chronic disease with great variability of survival time.

These authors were of the opinion that radical operation before metastasis has occurred gives the best prognosis. In so far as the operative words are "before metastasis" that is undoubtedly true and indeed platitudinous. The real question is, does radical operation give a better prognosis than nonradical operation or, indeed, than no operation at all if there is the possibility that distant metastasis, if it is going to occur, always occurs before operation is performed.

Geschickter (1947) said (p. 405):

"In general, it is impossible to estimate the influence of delay on prognosis unless the more malignant infiltrating cancers are separated from the more slowly growing, circumscribed forms .... If, however, the duration of symptoms and percentage of five-year survivals is calculated separately for individual pathologic types of cancer, the unfavorable effect of delay is apparent.

"In our own cases we have separated the infiltrating from the circumscribed forms (Table XLIX). The more circumscribed and slowly growing cancers have a longer duration of symptoms, averaging 17.5 months. In this group, the five-year survival rate is from 55 to 76 per cent. On the other hand, in the more rapidly growing, infiltrating cancers, the average duration of symptoms is 10.0 months, and the five-year survivals 32.6 per cent. Among these cases, women with cancer measuring 1 to 5 cm. in size had an average duration of symptoms of 8.5 months, with 42.8 per cent of five-year survivals; whereas those with larger tumors of the same type had an average duration of 14 months and a five-year survival rate of only 9.3%."

It is of course true that the real influence of delay on prognosis will be seen most clearly when the influences of growth rate on duration before treatment and on prognosis have been allowed for. One way of doing this would be to divide all the cancers into subgroups according to their intrinsic malignancies and, within each subgroup, to find the relation found between increased duration (or delay) and diminished curability; that is, with the growth rate "fixed." This procedure is, however, vitiated if the assessment of intrinsic malignancy is not independent of the duration be-

fore treatment; if, for example, tumors are put in the slow growing group *because* they have a long duration or *because* of some factor which includes duration as a biasing element. The size of the tumor (which is roughly growth rate × duration) is certainly such an element. It is not clear from the text that this has been recognized.

This author gave a diagram (Fig. 336B) showing the decrease in the percentage of 5 year survivals with increase in the duration of symptoms for each of the different forms of mammary carcinoma — infiltrating, transitional cell, and circumscribed carcinomas. In the infiltrating form (966 cases here) it appeared that the 5 year survival rate fell from 80 per cent at 2 months' delay to 22 per cent at 12 months and 3 per cent at 18 months. In the circumscribed form (386 cases here) it fell from 95 per cent at 2 months' delay to 77 per cent and 62 per cent, respectively. Now, the infiltrating form (p. 394) comprised 1,906 of the 2,499 carcinomas of this author's whole series, and the main bulk of it. If the relation between delay in treatment and fall in survival rate were as close as this in a group comprising three-quarters of the whole series, it would certainly be detectable, although of course less obviously, in the series as a whole. This is incompatible with the opening sentence of the quotation. If the influence of delay on curability could be proved as easily as this, there would be no need to investigate the matter at all.

It is not, we think, general experience that 80 per cent of the common scirrhous carcinomas of the breast diagnosed within 2 months of onset of symptoms show 5 year survival or that the survival rate drops from 80 to 22 per cent with a further 10 months' delay in treatment. These figures are quite unacceptable.

Haagensen and Stout (1942) gave a table (Table XVI) relating the results of radical mastectomy in primary cases to the duration of the disease on admission. The 5 year clinical cure rate was 54.0 per cent when this duration was less than 2 weeks, and 34.0, 40.0, 35.7, 28.6, 26.7, and 22.2 per cent when the durations were 2 weeks to 1 month, 1 to 2 months, 3 to 5 months, 6 to 11 months, 12 to 23 months, and 24 to 35 months, respectively, rising to 42.1 per cent with durations of 36 months plus. Their Table XVII related the duration of the disease on admission in primary cases to the presence of axillary metastases. The incidence of axillary metastases per cent was 50.0, 60.3, and 68.0 as the durations were, less than 1 month, 1 to 5 months, and 6 months or more, respectively.

We shall also mention here their tables (Tables XI and XII) relevant to the influence of biopsy on the results of radical mastectomy in primary cases. After 401 operations in which no biopsy was done the 5 year clinical cure rate was 27.9 per cent while after 220 operations at which biopsy was done the 5 year clinical cure rate was 50.0 per cent.

They said (p. 809):

> "From these data it is hardly fair to draw any conclusion because biopsy is more often done in the early than in the advanced cases, and the prognosis is, of course, better in this early group of cases. In order to exclude this disturbing factor we have prepared Table XII, which includes only those cases in which the primary tumor measured more than two centimeters in diameter (pathologic measurements) and yet was operable according to the criteria which today we rely upon. Thus, the earliest, as well as the most advanced cases, have been excluded."

Their Table XII shows that after 234 operations in which there was no biopsy the 5 year clinical cure rate was 33.8 per cent and after 123 operations with biopsy at operation the 5 year clinical cure rate was 49.6 per cent. They ended this section with the remark "From these data it would appear that biopsy does not prejudice the end-results of radical mastectomy."

There can be no quarrel with this conclusion since it has not been seriously suggested that the effect of biopsy may be to increase the survival rate, nor with the assumption that the raising of the 5 year clinical cure rate from 28 to 50 per cent after biopsy is false and due to a biased selection of doubtful cases for biopsy. It is unlikely that the effect of earliness of treatment per se would be sufficient to raise the 5 year clinical cure rate by this great amount. This effect would have to be at least 22 per cent and certainly much more since biopsies would not have been done exclusively

in very early cases although perhaps preferentially so. The doubt which made biopsy advisable in many and probably most of these cases must be attributed not to the earliness of diagnosis but to the lowness of the grade of malignancy and the slow growth rate, which in turn would be reflected in selective survival over the 5 year line and perhaps in greater curability.

The real point is, however, that it was only because these figures were obviously "impossible" that an attempt was made to discover *a posteriori* a reason why they were impossible. If the difference had been in the opposite sense, would this not have been accepted as unequivocal evidence of the dangers of biopsy? Moreover, the attempt was only partially successful and the substantial difference between 33.8 per cent and 49.6 per cent was left. It could be ignored in this instance but to ignore it is to deny the validity of all inferences based on differences of survival rates of less than 16 per cent.

We have taken this example from this excellent and classical article to demonstrate the complete futility of the 5 year cure rate as a measure of the effect of treatment in cancer of the breast and that, unfortunately, means the complete futility of most of the literature dealing with the treatment of cancer of the breast. A survival rate is an unsatisfactory statistic at the best. When the tumor type is as variable in its malignancy as is cancer of the breast, and when in addition the date chosen is well within the range of survival time of both untreated and treated uncured cancers, it is still less satisfactory. Moreover, the relevant literature is concerned almost entirely with the selected group of cases of that degree of malignancy which makes them suitable for operation—rarely with any attempt at definition of the amount or direction of the selection.

Hawkins (1944) in an evaluation of breast cancer therapy as a guide to prognosis said (p. 450):

"The duration of the disease at first treatment is shown in figure 1 for white females, Negro females, and white males. The mean duration for white females was 15.2, and for Negro females 22.6 months. Figure 1 shows that the cases may be divided into three rather equal groups: 4 months or less, 5 to 12 months, and 13 months or longer. In table 4 the status of these patients, based on their history of duration of the disease, is shown 5 years after first treatment. Although significant correlations existed between the duration of the disease and the stage of the disease at first treatment, the duration of the disease was not correlated with survival rates when corrections were made for the stage of the disease. Thus, patients having a history of shorter duration tended to have earlier stages of cancer than did those with long histories; but duration per se contributed little to the determination of prognosis which could not be more directly established by considering only the stage of disease at first treatment. At least two essential features contributed to this situation. Many patients are only vaguely familiar with the onset of their cancers; different cancers vary in their rate of growth, some grow rapidly and metastasize early while others grow slowly and may remain localized for years. If it were possible to determine accurately the onset and to correct for growth rate and for tendency to metastasize, the correlation between duration and survival would be much more striking than is here observed. The lack of such demonstration, however, does not detract from the obvious fact that for each cancer patient the earlier the treatment is begun the more favorable is the chance of cure."

Hawkins' Table 4 shows that of patients with a duration of disease of less than 5 months before treatment, 61.1 per cent died before the end of 5 years after first treatment; the corresponding figures for durations of 5 to 12 months and 13 months or longer are 70.3 per cent and 68.9 per cent, respectively. We may comment on the last sentence of this quotation that the lack of such demonstration does indeed detract from the otherwise unproved assumption that the earlier the treatment is begun the more favorable is the chance of cure.

McGraw (1947) discussed the prognosis after survival for 5 years or longer in women who had undergone radical mastectomy. He said (p. 295):

"We have scrutinized our data on the 8 patients whose recurrence or metastases appeared ten or more years after operation without discovering any dependable clues to the extraordinarily protracted quiescence of their microscopic foci of cancer which remained after operation. . . . Of the 8, only 2 were operated on within a month after they had first noticed their growth; 2 others had the operation one year afterward. Four had involvement of axillary nodes; 5 had retraction of the skin or the nipple or of both. . . . The only uniform factor in the clinical findings or in the treatment of these 8

women was primary operative closure of the wound without a skin graft. . . . [on p. 297] The data on the 12 patients of this group who have lived twenty years and over were examined to see whether their clinical and operative observations gave an especially good theoretic prognosis of a long survival. Favorable factors were that one half had operations less than one month after noticing their tumor and that two thirds were free of axillary involvement."

Nathanson and Welch (1936) in a discussion of the life expectancy and incidence of carcinoma of the breast said (p. 49):

"The delay from onset of symptoms has been studied in the group of patients entering the Huntington Hospital during the years 1923–32. Among these 690 cases the delay was accurately known in 575. Other cases were discarded. In this group the average delay was 1.05 years, slightly higher than that noted in the Massachusetts General Hospital series by Simmons in 1930, 0.85 year. In 1921 from the same hospital Simmons found that the delay to entry was one year.

It is unjustifiable to draw any conclusion from our figures concerning the importance of delay in determining the prognosis. They show that patients with the shortest delay to treatment have the worst prognosis. This means that patients with slowly growing tumors seek medical aid much later than those with rapidly growing tumors."

Richards (1948) said (p. 109):

". . . . the results which may be achieved by surgical methods provide the criterion against which all other methods must be measured. . . . [p. 110] Unfortunately, in spite of the vast literature available, a satisfactory answer as to the actual cure-rate by surgery is not easy to obtain, and in the past the figures could be used to prove almost any point of view held by the individual writing. . . . It seems safe to conclude that the average gross survival rate lies somewhere between the 22.2 per cent quoted by Haagensen and Stout and 36.9 per cent of Geschickter. But these figures are taken almost exclusively from highly specialized surgical clinics and, therefore, represent either the best results being obtained or, at least, the highest general averages."

In a section on the influence of size and duration of the tumor on curability he remarked that size and duration have an important bearing on prognosis, and gave a table (Table VI) relating rate of growth to survival. When the rate of growth was slow (less than 1 cm. per 6 months), moderate (1 cm. per 6 months), fast (more than 1 cm. per 3 months) and rapid (inflammatory), the 5 year survival rates were respectively 84, 63.5, 18, and 4 per cent. The numbers of cases on which each of these percentages was based was respectively 55, 104, 139, and 26.

The question is, of course, what would have been the 5 year survival rates of each of these subclasses if the tumors had not been treated. In any case, it will be seen that slight variations in the proportions of tumors of different growth rates will greatly affect the overall survival rate.

He also suggested a revival with modifications of the "Clinical Index of Malignancy" originally proposed by Lee and Stubenbord in 1928. The essential feature of such indexes is the allocation to each factor (or subgroup of each factor) of the weighting found empirically to be best fitted to the prognostic value of this factor. At its best—and the conditions of cancer prognosis are peculiarly suited to its use—such an index retains the accurately defined probabilities of a series of cases instead of the vaguely remembered clinical impressions based on these probabilities, and combines these probabilities in what has been found to be mathematically the most efficient way instead of by a process of irrational intuition.

Formal symbolism of this kind has never been accepted by the medical profession as a substitute for clinical judgment although it is, on the face of it, a rational and scientific way of thinking and achieving knowledge of truth. No doubt, the instinct which rejected it was wise. A sick human being is more than the sum of the signs and symptoms his physician can detect and describe quantitatively and there is no folly like the scientific folly which applies highly conditional generalizations unconditionally to the complex facts of human nature, society, and medicine. On the other hand some general rules and laws there must be if medicine is to be a science at all and the point is that the treatment of cancer is that branch of medicine which, above all others, uses a scientific discipline. We do not treat a woman with a lump in the breast as an individual cancerous patient on whom skill and craftsmanship suited to the individual problem should be applied. We treat her as a unit in the class of cancer of the breast with the assumption that all units of the class are

equally subject to three or four rules of probable behavior which have been found empirically to hold for the class regarded as an aggregate of equal units. This may or may not be a good thing, the probabilities may be spurious, the reasoning may be formally bad; but that is what we do and it must be better to reason accurately than inaccurately.

We will give an example of what we mean. One of us recently had to examine, in the course of his routine duties, a calcifying carcinoma of the rectum removed from a woman of 33 years. The surgeon remarked that "the prognosis was very very bad. She was a young woman; it was a colloid cancer." Now, that opinion would have been more accurate although equally right or wrong, if he had said "A's figures show that the survival rate of rectal carcinomas in women aged 33 is, say, 20 per cent and B found that colloid cancers have a survival rate of, say, 15 per cent and it has been found by C who worked out a clinical index of malignancy for cancer of the rectum that these two probabilities are independent, so that the probability that this patient will survive is 3 per cent (0.03)." In actual fact the tumor was lobular, demarcated, and extensively calcified, and there were no secondary deposits—findings which might well have suggested a good prognosis, so that an intuitive judgment formed on unanalyzed "general experience" might not have made the prognosis so very bad. But the point, here again, is that the surgeon's opinion of the prognosis was a scientific mathematical opinion uniting two mathematically defined probabilities with the assumption of a certain formal relation between them, and excluding all other probabilities. It might be suspected that the premises on which we reason are incorrect, inaccurate or incomplete, but to reason inaccurately where we might reason accurately will not compensate for these suspected fallacies. It will only add one more inaccuracy and fallacy.

With regard to the "Clinical Index of Malignancy" we ourselves would assess the position as follows. The arguments against this excellent procedure are essentially: (1) that the factors will not be found accurately—this is a matter of arithmetic—and (2) that there may be other recognized factors bearing upon the prognosis which are not measurable. We doubt whether there are such other unmeasurable factors in the intuitive reasoning by which a surgeon arrives at a prognosis in cancer of the breast. If there are, their presence will only to that extent diminish the value of the index, but it must still remain of positive value.

Robinson (1948) gave a table (Table II) comparing in Groups I and II the duration of symptoms in months before admission to the 5 year survivals and deaths. (Group I—carcinoma confined to the breast; group II—with metastases to axillary nodes only; group III—metastases beyond the axillary nodes; group IV—hopeless cases). In group I cases, the average duration before admission of the 5 year survivals was 11.3 months and of the cases in which death occurred, 12.1 months. In group II cases the corresponding figures were 9.9 and 12.3 months. The average ages in the group I cases were 52.4 and 55.1 years and in the group II cases, 52.7 and 50.3 years. He said "Comparing five-year survivals in Groups I and II the duration of symptoms before admission showed no significant difference (Table II)."

The following are quotations taken from a review of the literature of cancer of the breast made by Taylor in 1932:

"The average pre-operative duration in various series of cases ranged from nine to eighteen months. Many authors agreed with Bloodgood and Primrose that patients are reporting earlier, that the operability of cancer is increasing, and that the ratio of benign to malignant conditions shows some increase" [p. 4].

"Lee, in a series of 133 cases which were inoperable at the time of examination, found that in 30 per cent, the average duration of symptoms was four months, while in 52 per cent it was ten months. *These figures suggest that in a large proportion of any operative series of cases the disease is of a slowly growing type, and that in an inoperable series of cases the reverse is true*" [p. 7, Taylor's italics.].

"Stanton emphasized that the term early operation should be used to mean early in relation to the extent of the disease rather than in relation to the pre-operative duration of the disease" [p. 9].

[Referring to Lee and Stubenbord's "Clinical Index of Malignancy" (p. 12)]:

"The value of the clinical index is reduced also by the fact that it does not permit comparisons between different clinics because the individual fac-

tors, age groups, etc. may vary considerably, and yet, by reciprocal variations in other factors an identical index might be reached."

Taylor and Wallace (1947), in a report giving the end results following operation for carcinoma of the breast, stated (p. 476): "The cases of short duration show a definitely greater curability rate than those of longer duration."

Taylor and Nathanson (1942) discussing the duration of the primary carcinoma of the breast in its relation to lymph node metastasis said (p. 100):

"In various studies of end results in breast carcinoma cases treated at the Massachusetts General Hospital an attempt has been made to correlate the incidence of axillary metastasis with the duration of the disease before operation. In the series treated in 1927–1929 it was found that the median duration for cases without axillary metastasis was 3 months, while that for cases with axillary metastasis was 6 months. Corresponding figures for the series treated in the following period (1930–1932) were 2.8 months and 5.3 months, respectively.

"The duration of the disease before operation is of relatively little significance in relation to node involvement and prognosis in considering a large series of cases, but of the utmost significance in the individual case. The prognosis has always been found to be worse when the cases of short duration are segregated for special consideration. This may be explained, in part at least, by the fact that the highly malignant tumors are of rapid growth and attain a size which causes the patient to seek medical advice relatively quickly. Conversely the cases which are considered to be operable although of long duration include a relatively large number of patients with carcinomas of low degree of malignancy. When the pathological grade of malignancy is considered in relation to duration, it is found that a large proportion of cases of high grade malignancy which are submitted to operation are of less than 6 months' duration. It is to be inferred that the average case of high grade of malignancy of more than 6 months' duration has already progressed to an extent which renders it inoperable."

The natural duration of cancer of the breast. This, for obvious reasons, can only be measured directly on untreated patients. In many or most cases such lesions will not have been treated because treatment was considered hopeless and in the remainder it will be difficult to be sure that the reasons for nontreatment were not partly conditioned by the grade of malignancy of the tumor. Also it will be very probable that the diagnosis was definitely established for the cases in each published series by the later behavior of the tumor and that the manifestations of the tumor were unequivocally "malignant." There will be no doubtful diagnosis. It follows that such series will be made up of cases selected toward the more malignant grades of malignancy and growth rate. They will not be strictly comparable with series of treated cases which will tend to be of less malignancy and to contain an unknown proportion of tumors on the margin of malignancy or not malignant at all although necessarily treated as such.

TABLE I.—NATURAL DURATION OF UNTREATED BREAST CANCER, FROM ONSET OF SYMPTOMS TO DEATH*

Duration years	No. exposed to risk	No. deaths	Death rate	No. survivors
0	651	110	.169	1000
1	541	181	.335	831± 14.7
2	360	136	.378	553± 19.5
3	224	69	.308	344± 18.6
4	155	50	.323	238± 16.7
5	105	27	.257	161± 14.4
6	78	18	.231	120± 12.7

*From Table 5 of Greenwood (1926).
Mean duration (whole series) 38.3 months, standard deviation 43.3.

Table I is quoted from Greenwood (1926) and summarizes in life table form the natural duration, from the onset of symptoms to death, of the patients with untreated cancer of the breast.

Although obviously incomplete, the foregoing is a fair and representative sample of the literature referring to the absolute curability of cancer of the breast. The following is, we think, a fair summary of the inferences to be reasonably drawn from this sample.

1. Cancer of the breast has a wide range of variability in behavior, at least in so far as concerns the durations between the stages of growth and spread.

2. The series of cases which are mostly taken for study lie selected toward the lower grades of malignancy. Operable cases tend to be less extensive and cases which do not reach the surgeon at all tend to be "advanced" and very extensive. Slow growing cancers tend to be less extensive and fast growing cancers more extensive at the time of diagnosis.

3. The criterion of curability, the 5 year cure or survival rate, is unfortunately that form of test and that chosen critical date which most distortingly reflects and magnifies variations in the proportions of different grades of malignancy in the cancers treated.

4. No valid comparison can be made between the results of different treatments assessed in conventional ways or between the results of series of tumors treated and not treated. That is, the differences observed are of the same order of magnitude as those which might well be due to chance and selective bias.

5. Although not conclusively so, there does seem to be some evidence that increased delay in treatment may slightly decrease the curability.

6. Although in theory the relation between delay in treatment and diminished curability will be more efficiently observed and defined when the obscuring effect of the differing growth rates are removed, in practice the technical difficulties of independently measuring growth rates seem to be very great. As judged by the extracts quoted, a clearer definition of this relation has not in fact been obtained.

7. If there is a relation between delay in treatment and curability, and, since present day treatment of cancer of the breast is based on the assumption that this relation does exist, if treatment is effective at all, it would be expected that this relation would be empirically demonstrable.

The relation has not in fact been demonstrated. This failure may be attributed partly to the inadequacy of our methods of measuring curability and partly to the variability inherent in the sampling of any very variable quantity. But the influence of the relation itself, if it exists, cannot be great or it would have been detected through these admittedly obscuring factors. As a guess, and no better is possible, the influence of delay in treatment upon the curability cannot be greater than 5 to 10 per cent; that is, earliness or lateness of treatment will raise or lower the overall curability rate by a maximum of 5 to 10 per cent. In other words, it has been demonstrated that the curability is not more than this, it may be less, and it may not exist at all.

It is one of the irritating deficiencies of the 5 year survival rate that it does nothing to distinguish between 100 per cent curability in 5 per cent of the cases, and 5 per cent "curability" in all of the cases. The sooner this discredited criterion of cure is abandoned the better.

PART III.—THE RELATION BETWEEN DELAY IN TREATMENT AND INCREASE IN INCIDENCE OF AXILLARY METASTASES

The presence or absence of axillary metastases is usually recorded at the time of removal of the primary growth. This means that the incidence of metastases after a given period of delay between onset of symptoms and time of treatment will contribute no help toward finding what would have been the incidence of metastases after this delay if the primary had been removed at the onset of symptoms, except that it would presumably not have been greater than that actually found.

As has been said, however, the relation between the delay in treatment and the increased incidence of metastases will give some idea of the time scale involved, whether this be regarded as the rate of spread of the malignant cells or the rate of appearance of the manifest lesions.

The following analysis is based on records made during routine histological diagnosis at the Royal College of Physicians' Laboratory Edinburgh, during the years 1939 to 1949. There were 814 cases in which the duration between onset of symptoms and date of diagnosis as well as the presence or absence of axillary lymph node metastases was known. Since 1947 the size of the tumors was recorded, so that, of these 814 cases, in 196 instances the size of the tumor was also known.

1. *Duration.* This had been recorded by the surgeon on the form accompanying the specimen. In some cases the actual time was not specified in number of months or weeks and there was some such wording as "recently," "few months," or "few weeks." In order that these cases be included, each of the phrases was allocated to what seemed the most reasonable of a series of time compartments.

2. *Size of tumor.* When the tissues were examined at the time of macroscopic section

the size and shape of the tumor had been expressed sometimes in the "large pigeon's egg"/"small walnut" terminology, sometimes as actual measured dimensions. Cancers of the breast are often irregular and infiltrative, and where this was the case the total bulk was expressed as the diameter of an equivalent sphere.

3. *Metastases.* These data refer, of course, only to cases in which axillary tissue had been removed and in which lymph nodes were found and sectioned for microscopic examination. How far there will be a systematic bias in subjecting patients with large tumors of long duration to radical mastectomy rather than simple mastectomy *for these reasons* we cannot say. Since lymph node metastases are most frequently found in microscopically examined axillary tissue it would follow that in so far as there was this bias toward radical mastectomy for these reasons, the correlation between increased tumor size and duration on the one hand, and the incidence of axillary metastases on the other, would be to that extent spurious. As things are, it is impossible to assess the presence or degree of this bias, but it probably exists to some extent; and will, therefore, to that extent exaggerate the correlation.

The important point is that in this investigation the assessing of the numerical value of each factor in each patient was made without immediate knowledge of the values of other factors within the patient. What hidden biases and selections there might be we cannot know.

The figures of the series are summarized in Tables II and III.

Taking the factors *duration* in months before treatment, *size* in centimeters diameter, *proportion of cases with invaded lymph nodes* as the percentage, we have worked out for each pair of factors:

The correlation coefficient. It is to be noted that although the maximum correlation coefficient with absolute correlation is 1 (or -1), a coefficient of 0.3 or even 0.6 does not denote a close association for practical purposes. It may be "significant" in the sense that it is very unlikely that the figures would have occurred by chance if there were no association at all; but the relation is not close in the sense that, if one factor in an individual case be given, the other factor is not thereby defined much better than if there were no association.

TABLE II.—DURATION OF BREAST CANCER AND INVASION OF AXILLARY LYMPH NODES AT TIME OF TREATMENT

Duration months	No. cases invaded	No. cases not invaded	Total No. cases
0–1	88	61	149
–2	89	47	136
–3	61	31	92
–4	24	22	46
–6	80	44	124
–9	28	10	38
12	72	24	96
13–18	20	8	28
19–24	37	12	49
25–36	12	5	17
37–60	17	3	20
60+	14	5	19
Total No. cases	542	272	814

The regression equation.[1] This summarizes the trend of the way one factor changes as the other factor changes.

Table II gives the incidence of axillary metastases at different durations after the onset of symptoms and Table III this incidence at different sizes of the primary tumor.

TABLE III.—DIAMETER OF PRIMARY TUMOR AND INVASION OF AXILLARY LYMPH NODES AT TIME OF TREATMENT

Diameter mm.	No. cases invaded	No. cases not invaded	Total No. cases	Percentage invaded
0–11	7	2	9	78
–20	24	15	39	62
–30	42	22	64	66
–40	29	3	32	91
–50	5	6	11	45
–60	23		23	100
–70	10		10	100
–80	5	1	6	83
–90	1	1	2	50
Total No. cases	146	50	196	

[1]We have calculated the regressions without "transforming" the proportions of cases with lymph nodes invaded. Technically this is incorrect but no more is necessary here.

The relations between these factors are described as follows:

A. Duration after onset of symptoms in months = x
Percentage of cases with axillary invasion = y
(814 cases in all)
The correlation coefficient is 0.56.
The best fitting regression line is, $y = 0.24x + 63.6$.
That is—at onset of symptoms the percentage of cases showing axillary metastases is 63.6
at 12 months delay it is 66.5
at 24 months delay it is 69.4
at 36 months delay it is 72.2.

B. Duration after onset of symptoms in $\log_{10}$ months = x
Percentage of cases with axillary invasion = y
(814 cases in all)
The correlation coefficient is 0.70.
The best fitting regression line is, $y = 9.9x + 59.4$.
That is, at onset of symptoms the percentage of cases showing axillary metastases is 59.4
at 12 months delay it is 70.1
at 24 months delay it is 73.1
at 36 months delay it is 74.8.

C. Diameter of tumor in cm. = x
Percentage with axillary invasion = y
(196 cases in all)
The correlation coefficient is 0.52.
The best fitting regression line is, $y = 4.79x + 56.7$.
When the tumor is 1 cm. in diameter the percentage of cases showing axillary metastases is 61.5.
When the tumor is 5 cm. in diameter the percentage of cases showing axillary metastases is 80.7.

D. Duration after onset of symptoms in months = x
Diameter of tumor in mm. = y
(196 cases in all)
The correlation coefficient is 0.30.
The best fitting regression line is, $y = 0.33x + 30.35$.
That is—at the onset of symptoms the average diameter of the tumors is 3.04 cm.
at 12 months delay the average diameter is 3.43 cm.
at 24 months delay the average diameter is 3.83 cm.
at 36 months delay the average diameter is 4.22 cm.
a. For the 146 cases showing axillary invasion the correlation coefficient is 0.22 and the best fitting straight line regression is $y = 0.31x + 32.3$.
b. For the 50 cases not showing axillary invasion the correlation coefficient is 0.24 and the best fitting regression line is $y = 0.33x + 25.5$.
All the correlations are "significant" by the conventional standard with the exception of the last.

We have not attempted to find more than the simple "straight line" relation between each pair of factors, in order to show the trend of each relation and whether this trend was statistically significant; and also to gain some idea of its quantitative values. These figures although no worse than most such, are not accurate or reliable enough to justify more rigorous treatment.

We can, however, draw some cautious inferences from these figures, as follows:

1. a. About 60 per cent of patients with diagnosed cancer of the breast have microscopically detectable axillary metastases at the time of onset of symptoms.

b. There is an increase in the incidence of such metastases with increased duration of the tumor after onset of symptoms. This increase is of the order of 12 to 15 per cent over the first 3 years.

c. About 20 to 30 per cent of patients with diagnosed cancer of the breast do not develop axillary metastases within 3 years of onset of symptoms. Whether that means that these patients will never develop axillary metastases or whether the incidence will increase by 5 per cent (of the total patients) per annum after the third year cannot be deduced from these figures. The answer will depend on whether the relation between duration and incidence is better described by the procedure of A or B given previously. The difficulty is that the relation, as exhibited here, is almost certainly distorted by a bias for slow growing tumors to have a longer delay before diagnosis just because they are slow growing.

2. The average rate of increase in the diameter of the tumor during the period after onset of symptoms is known, and it might be hoped that by "producing the curve backward" one could find how long it would have taken the tumor, starting from a very small size, to reach the actual size found at the time of diagnosis. The difficulty is that the figures are so variable that it would not be possible to define with any accuracy the law which relates the increase in size to the time; and in any case this relation may be different in the early stages of a cancer from what it is in later stages.

a. Our figures show that the average diameter of the tumor increases by 0.4 centimeter with each year's delay in treatment. This rate of growth is probably artificially low because of the bias in the collection of the figures already mentioned. We may, however, take the

estimate of Richards (1948) that tumors of moderate growth increase their diameter by 1 centimeter per 6 months. This figure refers to the clinical measurement which is, he says, approximately twice the diameter of the pathological specimen. Let us say that the average tumor has a constant rate of cell increase (i.e. its volume increases by geometrical progression and logarithmically), and that this rate is such that the diameter increases from 3 to 3.5 centimeters during the 6 months after the onset of symptoms. Under these conditions it would take 8 years for the tumor to grow from 2 millimeters to 3 centimeters in diameter. Such calculations are, of course, complicated by all kinds of other factors, such as the amount of necrosis and fibrosis associated with the tumor, which have to be ignored. It does seem, however, that any attempt to work backward along these lines from the observable data leads us to a duration of the cancer of several years before the onset of symptoms. This presumption is strikingly confirmed by the rate of increase in the incidence of axillary metastases.

b. The incidence of axillary metastases increases by 5 to 10 per cent during the year following onset of symptoms. If one assumes that this rate of increase is constant, then at a point 6 to 12 years before the date of diagnosis the incidence of axillary metastases would be nil. The alternative is to assume that the chances of axillary metastasis are not equal throughout the life of the tumor but are very great at some period just before the onset of symptoms.

Taking the two independently assessed factors together we would say that these figures point to an average duration for the tumor of many years before the onset of symptoms, and that the chances of metastatic "takes" are equal throughout this period. What, if any, is the duration before the probability of metastatic "take" assumes a significant level can only be guessed.

It is known that the average duration of life from onset of symptoms to death in patients with untreated cancer of the breast is 3 to 4 years. Taking the evidence as a whole, a fair estimate of the average duration of cancer of the breast from the date of assumption of metastasizing potential to death would be 8 to 10 years, with a variability which would make this duration 6 months in very rapidly growing cancers and longer than the natural expectation of life in slow growing cancers. That the interval between onset of symptoms and death is a relatively small proportion of the total life of the cancer is probably applicable to all cancer types. If a cell proliferation is doubling the number of its constituent cells in a given time, it will require many doublings for the total number of cells, starting from a small number, to produce the tumor size required to cause symptoms, and comparatively few doublings thereafter for the number of cells to increase from that required to cause symptoms to that required to kill.

3. There is an association between increased incidence of axillary metastases and increased delay in treatment, and also associations between each of these and increased size of tumor. It would clearly be desirable to know, which, if any, is the basic association of the three and we have in fact worked out the partial correlations (the correlation of each pair of factors with the other factor constant or fixed). This might have indicated which was the basic association but in fact nothing definite has resulted and we shall not give the figures.

PART IV.—THE RELATION BETWEEN INTRINSIC GROWTH RATE AND SURVIVAL TIME AND RATE

In order to discover the relation between incidence of axillary metastases, survival rate, and survival time of those dying we shall quote the figures given by Harrington (1941) who recorded the results obtained at the Mayo Clinic. We have used these figures since they form a very large and completely examined series; it is the only such series we have examined.

In his Table IV, Harrington gives the follow up findings in the cases of women who had undergone radical mastectomy for unilateral cancer of the breast. The tables give the number of patients operated upon, the number of patients traced (these are almost the same), and the proportion of traced patients surviving to those at risk at 3, 5, 10, 15, and 20 years after operation. These data are given for groups according to the histological grading

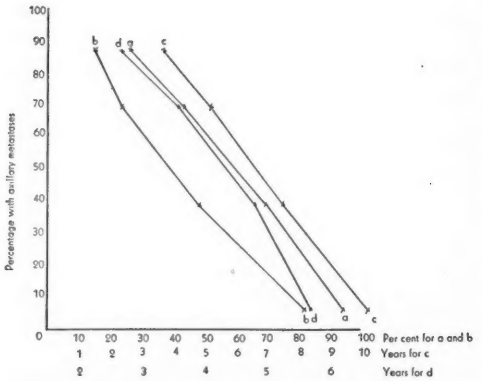

Fig. 4. Diagram showing relationship between incidence of axillary metastases, survival rate, and survival time of patients dying of cancer of breast. (Figures taken from Harrington's (8) Table IV.) *a*, Percentage 5 year survival rate; *b*, percentage 10 year survival rate; *c*, average survival time of those dying within 20 years; *d*, average survival time of those dying within 10 years.

and according to the presence or absence of axillary metastases. These data have been rearranged and further analyzed in Tables IV and V.

Figures 4 and 5 put these data in diagrammatic form.

The percentages of cases with axillary metastases have been calculated from the data of Harrington's Table IV. They differ slightly but not significantly from those given in his Table III which was based on more cases.

The mean survival times of those dying were found as follows: The proportion dying within 3 years was found from the 3 year survival rate and these were assumed to have died at an average of 1.5 years after operation. The proportion of those dying between the end of the third and the end of the fifth year was taken to be the difference between the 3 and 5 year survival rates and these were assumed to have died at an average of 4 years after operation. The proportion of women dying during each other interval was similarly found and the average times of death were assumed to be 7.5, 12.5, and 17.5 years after operation, respectively. The overall mean time of death was then easily found.

The survival rates and mean survival times of our Table IV, that is of all cases in each grade with and without metastases, have been calculated from the data of our Table V.

For example the grade III 5 year survival rate was,

$$\frac{824 \times 32.0 + 364 \times 66.8}{1188} = 42.7$$

The total cases are thus divided into four categories, and for each category there are: (a) a histological grading of malignancy; (b) a criterion of the intrinsic growth rate—the survival time of those patients dying within 20 years; (c) the conventional criterion of the effect of treatment—the 5 year survival rate; (d) the conventional index for prognosis—the proportion of cases with axillary metastases at the time of diagnosis.

The striking and important point and, indeed, the answer to the question whether radical mastectomy is effective at all, is that all these factors run parallel, as can be seen from Figure 4. By ordinary reasoning each is a function of the other, at least till the contrary be proved. The fundamental factor must be the intrinsic malignancy of the tumor whether this be assessed by histological grading or by the survival time of uncured patients. We may therefore say that, until the contrary has been proved, these figures indicate that the

TABLE IV.—RELATIONSHIP BETWEEN AXILLARY METASTASES, SURVIVAL RATE, AND SURVIVAL TIME*

Grade	Number of cases operated on	Percentage with axillary metastases at operation	Percentage 3 year survival rate	Percentage 5 year survival rate	Percentage 10 year survival rate	Mean survival time of those dying	
						Within 10 years in years	Within 20 years in years
I	160	6.9	96.3	94.4	82.7	5.7	10.2
II	475	39.8	80.4	69.3	46.7	4.8	7.5
III	1188	69.4	60.1	42.7	24.0	3.6	5.2
IV	1919	87.6	38.8	26.8	15.7	2.7	3.7

*Taken from Harrington's (1941) Table IV.

proportion of axillary metastases and the 5 year survival rate are secondary functions derived from the intrinsic malignancy or growth rate of the tumor: they can be adequately and completely explained as such, and there is no need to invoke the effect of treatment to explain them. The contribution of delay in treatment in increasing the incidence of metastases or diminishing the 5 year survival rate must be relatively small.

This is seen still more clearly in Table V and Figure 5. If the presence of metastases could be attributed in any significant degree to delay in treatment, and if delay in treatment resulted in a diminished 5 year survival rate, it would be expected that the groups of cases with axillary metastases would be shifted to the right and downward in Figure 5. There is a hint that this may be so but the effect, even if present, must be slight.

It might be argued that the survival time in patients dying of a cancer is not a good criterion of the intrinsic malignancy of the cancer, the implications being that the survival time in unsuccessfully treated patients is increased because of treatment, and that the effectiveness of treatment would be greater in those tumors without axillary metastases; and that the results could be explained in these terms.

Against this argument it may be said: (a) The 5 year survival rate is determined by the intrinsic malignancy equally as closely when this is assessed by histological grading as when it is assessed by the mean survival time. (b) The rational hope of surgical treatment is that it cures, not that it prolongs survival time, even though it may do so in unsuccessfully treated cases. The close association between mean survival time and survival rate shown in Figure 5 indicates that the 5 year survival rate can only be a function of the mean survival time. It might be that surgical treatment is effective only in so far as it increases survival time (and proportion of apparent cures) but it is not with that expectation that it is given.

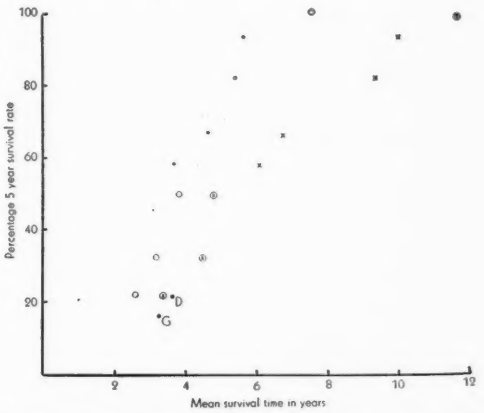

Fig. 5. Diagram showing relationship between 5 year survival rate and mean survival time of those dying: ⊙, within 10 years with metastases at time of operation, . those without metastases; ⊗ within 20 years with metastases at time of operation, × without metastases.

It is interesting to note how the data obtained from series of cases of untreated cancer of the breast fit into Figures 4 and 5. In the series reported by Daland (1927) of 100 patients with cancer of the breast who had received no treatment, the 3 year survival rate was 40 per cent, the 5 year survival rate was 22 per cent, and the mean duration of life

TABLE V.—RELATIONSHIP BETWEEN METASTASES, SURVIVAL RATE, AND SURVIVAL TIME*

Grade	With or without metastases	Number of cases operated on	Percentage 3 year survival rate	Percentage 5 year survival rate	Percentage 10 year survival rate	Mean survival time of those dying	
						Within 10 years	Within 20 years
I	with	11	100.0 (1)	100.0 (1)	70.0 (2)	7.5 (1)	11.7 (1)
	without	149	96.0 (2)	94.0 (2)	83.6 (1)	5.6 (2)	10.1 (2)
II	with	189	66.7 (6)	50.0 (6)	29.7 (6)	3.8 (5)	4.8 (6)
	without	286	89.5 (3)	82.1 (3)	57.9 (3)	5.4 (3)	9.3 (3)
III	with	824	50.6 (7)	32.0 (7)	15.2 (7)	3.2 (7)	4.5 (7)
	without	364	81.6 (4)	66.8 (4)	43.9 (4)	4.6 (4)	6.8 (4)
IV	with	1682	34.5 (8)	22.4 (8)	12.1 (8)	2.6 (8)	3.4 (8)
	without	237	69.6 (5)	58.1 (5)	41.2 (5)	3.7 (6)	6.1 (5)

*Taken from Harrington's (1941) Table IV.

from onset of symptoms was 40.5 months. Greenwood (1926) gave similar records for 651 patients; the corresponding figures were 34.4 per cent, 16.1 per cent, and 38.3 months.

These relations between 5 year survival rate and mean survival time have been included in Figure 5 as points *D* and *G*, respectively. It will be seen that they fit fairly well.

When the figures for 5 year survival rate are plotted into Figure 4, line *a*, they are found to correspond to an incidence of axillary metastases at time of diagnosis of 91 per cent in Daland's cases and 98 per cent in those of Greenwood. Similarly the figures for mean survival time, taking for these the mean survival times of those dying within 20 years (line *c*), correspond to an incidence of axillary metastases at time of diagnosis of 93 per cent and 95 per cent, respectively.

In reviewing the figures mentioned it must be remembered that the variability due to chance is relatively high in any simple proportion, and that, although Harrington's series which we have quoted is large, the main bulk of the series lies in grades III and IV. The number of deaths within 20 years in cases classified as grade I with metastases is only 8, and within 5 years in grade I without metastases the number is only 9.

We may conclude this section of the paper by saying that undoubtedly the simplest and, in our opinion, the only explanation for these results is as follows:

There is a great variability in growth rates between individual cancers of the breast. The more rapid the growth rate, on the average, (a) the earlier the onset of symptoms in the life of the cancer; (b) the larger the size of the primary tumor at the time of diagnosis; (c) the shorter the delay between onset of symptoms and diagnosis; (d) the sooner the development of axillary and other metastases; (e) the higher the incidence of detectable axillary metastases at the time of diagnosis; (f) the less the 3, 5, 10, 15, and 20 year survival rates; (g) the less the mean survival time of those dying within 3, 5, 10, 15, and 20 years after diagnosis; (h) the higher the histological grading of malignancy.

All the evidence available can be explained in terms of the above tenets. There is no additional evidence which would require effectiveness of treatment as an explanation. There is sufficient evidence to show that such effectiveness, if it exists at all, can be no greater than negligible.

A suggested index of curability of breast cancer. It is clear that the most urgent need of present day cancer treatment is some better method of measuring the effect of that treatment.

The defects of the 5 year survival rate as applied to cancer of the breast are essentially two: (a) The great variability of growth rates means that no two series of cases ever contain the same proportions of cases of different degrees of malignancy, nor of patients who would have survived for 5 years in any event, with or without treatment. (b) If all the cases could be sharply divided into two groups, cured and uncured, and if the presence or absence of 5 year survival were synonymous with cure, we could not do better than use the 5 year survival rate. If, however, there are degrees of curability, to use only the number of cases on either side of an arbitrarily drawn dividing line must mean a great loss of available information.

The first difficulty may be partly overcome by using the proportion of cases with axillary metastases at the time of diagnosis as an index of the proportions of different "malignancies" present in the series.

From the data of Figure 4 we learn that,

if y is the percentage incidence of axillary metastases

and x is the percentage death rate (i.e. 100 minus percentage survival rate) for all grades of malignancy,

$$\frac{x}{y}=0.83 \text{ for the 5 year survival rate.}$$

That is, for patients with breast cancer treated by radical mastectomy and, we suggest, for patients with untreated breast cancer, the number of patients dying of cancer within 5 years is eight-tenths of the number with axillary metastases at the time of diagnosis, for all grades of malignancy. A method of treatment would be effective in so far as it gave a statistically significant fewer number of deaths.

The merit of this index is not only that it is as accurate as the straightness of the line in

Figure 4 but also that it internally compensates for an excess of low grade or nonmalignant tumors (i.e. tumors with neither axillary metastases at the time of diagnosis nor sequential death from cancer within 5 or other number of years): that is, it internally compensates for an undue extension of the lines in Figure 4 beyond the abscissa. The figures given for untreated cancer suggest that the lines of Figure 4 do not extend beyond the ordinate, and that the range of the line drawn is the farthest it extends in this direction.

The factor of curability applies, of course, only if the cases with axillary metastases are not specially selected as such. In other words, although there is roughly one 5 year death for each case with axillary metastases they are not necessarily the same cases. The factor allows for differences in the proportion of cases within each grade of malignancy so long as the grade of malignancy is not itself assessed by the presence or absence of metastases. Thus, if stage I cases are those without metastases and stage II cases those with metastases, it is obvious that the factor cannot be applied to stage I cases or stage II cases taken separately. It will, however, give the 5 year survival rate to be expected with that ratio of stage I to stage II cases.

The second defect of the 5 year survival rate mentioned can be overcome by an extension of the same principle.

The deduction that cancers are either completely cured or completely uncured follows from the theory of cancer behavior on which surgical treatment is based; but that theory is almost certainly artificially narrow and incomplete. If ever a treatment is found for cancer which is completely curative we shall not need to study methods of best demonstrating its curative powers. If, however, treatments are found which are partly curative it is practically certain that this partial curability will not be expressible as an atomistic number of cases completely cured or completely uncured; it will be expressible in terms of cases each partially cured, more or less.

For the assessment of cancer therapy we have at the moment no criterion of partial curability except the time of survival to death, or rather the excess of this survival time due to treatment over the untreated survival time for that grade of malignancy.

Figures 4 and 5 show the closeness of the relation between histological grade of malignancy, survival rate, and the mean survival time of those patients dying within 10 and within 20 years of operation. Although the figures are not available to confirm it, it seems most likely that this close relation will also hold for the mean survival times of deaths occurring within 3 years and 5 years of operation. Such a mean survival time, since it makes use of much more information than a survival rate, will be correspondingly more sensitive. The significance of deviations from the standard mean survival time will also be much more easily found. Each grade of malignancy will have its own standard mean survival time, but we can use, as before, the incidence of axillary metastases at the time of diagnosis as an index of the proportion of different grades of malignancy within the series. The relation between the percentage of axillary metastases and the mean survival time of deaths occurring within 3 years or 5 years can be expressed as a single figure if the relation lends itself to expression in this way or, at the worst, it can be expressed graphically.

For a series of cases of cancer of the breast it would thus be known, from the proportion of cases with axillary metastases, what mean survival time could be expected in untreated cases (or in cases submitted to radical mastectomy) with that average grade of malignancy. This would be the standard for comparison. The effectiveness of treatment, in so far as it prolonged the mean survival time in patients dying within 3 or 5 years, would be recognized by a significant increase in the mean survival time. As we have said, it seems highly probable that any treatment which was effective at all would prolong the mean survival time, even in ultimately uncured cases.

SUMMARY AND CONCLUSIONS

1. The treatment of cancer of the breast is based on the hypothesis that earliness of treatment increases the cure rate. We are rationally entitled to judge the effectiveness of that treatment on the same basis. It follows that the only direct evidence that such treatment

is effective will be the finding that delay in treatment does indeed diminish the cure rate. Examination of the literature showed that this direct evidence has not been found. This failure is due partly to the variability, and opportunity for biased observation, of estimates of the date of onset of symptoms, but in the main it is due to the great variability in growth rates between different cancers of the breast.

2. The maximum apparent curability has been found in two ways:

a. It was found that, in cancers of the breast diagnosed by conventional standards, the proportion of cases with axillary metastases at operation increased from 60 per cent, in patients operated on at the time of onset of symptoms, to about 75 per cent in those in whom operation had been delayed till 3 years after onset of symptoms. If current beliefs in the eradicability of cancer are accepted rigidly and the assumption is made that the cancer has already spread outside the zone of possible excision in 80 per cent of the cases with axillary metastases and in 30 per cent of the cases without, it will follow that the 5 year survival rate of those operated on at the onset of symptoms is 40.0 per cent, and of those operated on after a delay of 3 years 32.5 per cent.

The difference between these survival rates is the maximum apparent curability.

b. The literature shows that the difference between the 5 year survival rates of patients with mammary cancer who were treated and those who were not treated is about 20 per cent—also a maximum apparent curability.

3. It has been explained how variability in growth rate between different cancers combined with the use of a survival rate as a measure of cure can create an apparent cure rate which is partly or wholly fictitious. From an analysis of the evidence it has been shown that the apparent curability of cancer of the breast can be explained entirely in terms of the variability of growth rate.

4. The results of this examination of true curability of cancer of the breast can therefore be summarized as follows:

a. It has not been proved that the survival rate of cancer of the breast, using the 5 year survival rate as an index, is affected by treatment at all.

b. The evidence strongly suggests that treatment is quite ineffectual in reducing the incidence of death from metastatic spread.

c. If treatment is in any way effective, the effectiveness cannot be greater than that required to increase the overall 5 year survival rate by more than 5 to 10 per cent.

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LATE SEQUELAE OF INFERIOR VENA CAVA LIGATION

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LIGATION of the inferior vena cava has proved to be a most effective method of preventing pulmonary infarction due to venous thrombosis in the lower extremities or pelvis. In the last 10 years this procedure has gained considerable popularity after repeated clinical proof that ligation of this great vein below the renal vessels could produce such beneficial results in a patient whose life was threatened by multiple pulmonary infarctions. The technical performance of ligation is not difficult—it is well within the repertoire of the trained general surgeon, and has been carried out with a low mortality rate in all clinics despite the fact that the majority of the patients were dangerously ill.

It is, nevertheless, a formidable as well as effective procedure, and adverse sequelae can and do result in an appreciable number of cases. This has been emphatically brought to our attention by the repeated visits to our out-patient clinics of patients who have had vena cava ligation and present its sequelae. We were thus prompted to undertake the study reported here.

It should be pointed out that the socio-economic status of the majority of patients reported here was below average. In a city-county hospital, many patients are indigent, suffer chronic nutritional deficiencies, and have occupational handicaps. Their home care is frequently poor because of financial reasons or lack of understanding. These facts would seem to preclude a comparison of this group of patients with a group seen in private practice.

Between July 1943 and July 1950, the inferior vena cava was ligated in 37 patients at Grady Memorial Hospital (Fig. 1). The ages of these patients ranged from 15 to 64 years; the average age was 35 years, and 27, or 73 per cent, were in their third and fourth decades of life. There was almost identical distribution as to sex. Fourteen patients were white; 23 were negro. Both groups were under the supervision of the same physicians.

Prior to vena cava ligation, 5 of the patients had been treated with anticoagulants alone; 3 had been treated by bilateral superficial femoral vein ligations, and 2 with both anticoagulant therapy and femoral vein ligation. The remaining 27 patients had received only conservative therapy which consisted of rest, heat, elevation, and elastic bandages. The predisposing disease or surgical procedure is shown in Table I. All of these patients had suffered 1 or more pulmonary infarcts before ligation of the vena cava. There were 2 operative deaths in the 37 patients, a mortality rate of 5.4 per cent. The majority of the operations were performed by the resident surgical staff.

The hospital records of these 37 patients were reviewed, and a follow-up study was made of the patients who could be contacted. Of the original 37, 2 had died at operation, 3 had died later of unrelated conditions, and 7 had either left the city or did not answer inquiries. Thus, 25 patients remained for evaluation (Table II). Three of this group are registered nurses who live a great distance from this city. They were asked to answer by mail a detailed questionnaire, and their answers were included with the data on the group examined. Twenty-two patients were seen and examined.

The length of hospital stay of only 33 patients could be determined as the discharge date was not entered on the records of 4 patients. These 33 patients were hospitalized an average of 20 days following vena cava ligation, with 16 days of bed rest and elevation of the lower extremities. Twenty pa-

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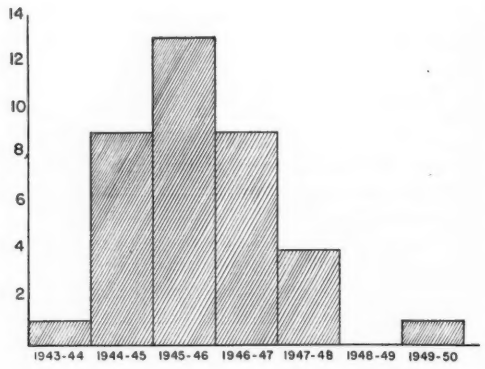

Fig. 1. Number of vena cava ligations performed per year.

tients used ace bandages throughout their hospital stay. The severity of the sequelae had little relation to the time spent in bed with elevation of the legs and the use of elastic stockings. Some of the patients with the fewest days of bed rest and elevation postoperatively had the least sequelae, but no definite correlation could be determined. Rest and elevation during the immediate postoperative period are believed to be important, but the observations recorded here do not indicate that such therapy will prevent sequelae or even modify them to any extent. This has been noted also in the patients subjected to prophylactic superficial femoral vein ligation (6).

TABLE I.—DISEASE OR SURGICAL PROCEDURE PREDISPOSING TO THROMBOEMBOLISM IN 37 CASES

Service	Reason for hospitalization	No. cases
Obstetrics and gynecology	Hysterectomy	5
	Parturition	5
	Acute pelvic inflammatory disease	1
Surgery	Spontaneous thrombophlebitis	5
	Appendectomy	3
	Transurethral resection	2
	Herniorrhaphy	1
Medicine	Pneumonia	4
	Cardiac decompensation	2
	Upper respiratory infection	1
	Lues (meningovascular)	1
Orthopedic	Fractures and/or dislocations	5
	Muscular strain	1
	Leg amputation	1

In a few patients, the manifestation of thrombophlebitis in the lower extremities was intensified following caval ligation. In most, these symptoms rapidly subsided after treatment by lumbar sympathetic block, elevation of the lower extremities, and bed rest.

Lumbar sympathectomy was performed on 4 patients at the time of vena cava ligation, unilateral in 3, and bilateral in 1. Seven other patients were subjected to repeated lumbar sympathetic block with procaine during the immediate postoperative period. While relief of leg pain from thrombophlebitis was obtained, there was no evidence that sequelae were prevented or delayed, nor was any effect observed on the venous pressure when measured. It was concluded that no beneficial effect, other than transient relief of phlebitic pain was obtained by either sympathectomy or lumbar block.

The number of visits to the surgical clinics for each patient varied from 2 to 27 during the period of this study, with an average of 7 visits per patient. However, this is an uncorrected value as 5 patients were free from major sequelae postoperatively, and the number of years the patients have been followed vary from 2 to 7.

Only 1 of the 25 patients questioned was free of complaints of changes in his physical well-being and the status of the lower extremities in particular. Thirteen patients noted a persistent increase in the size of their legs following ligation, not attributable to any weight gain. Twelve patients have never been without swelling of the legs since the postoperative period. The degree of severity varied evenly from moderate to extreme. Seven other patients complained of intermittent swelling of the legs, which usually becomes more severe toward the end of the day and disappears after a night's rest. The remaining 6 patients had no swelling at any time.

Two complaints, which when present were a source of great concern to the patient because they limited both his activity and em-

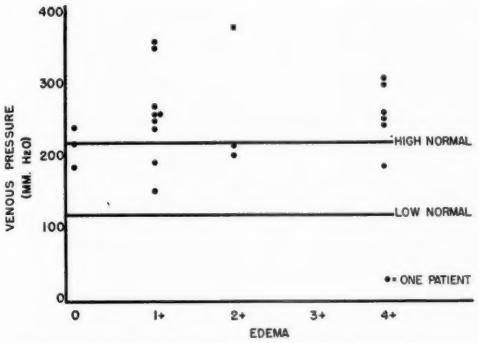

Fig. 2. Edema following vena cava ligation. No correlation is apparent between venous pressure and edema.

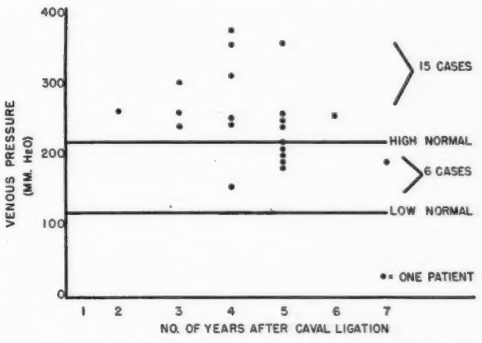

Fig. 3. Persistence of elevated venous pressure following vena cava ligation.

ployability, were easy fatigability of the legs and intermittent claudication. Twenty patients complained that their legs tired easily; 17 had intermittent claudication varying from mild to severe, and some of these had nocturnal cramps.

According to the hospital records, 26 of the 35 patients surviving ligation of the vena cava developed edema in the immediate postoperative period. Twenty of the 25 patients evaluated now have pitting edema of the lower extremities; in 2 the edema is unilateral. It varies from 1 to 4 plus, depending in most instances on how much the patient has been in the upright position and standing or walking. Four patients are free from edema at all times. This study corroborates an observation made previously by Ray and Burch (5) that edema is not necessarily associated with elevated venous pressure (Figs. 2 and 3).

Ten patients developed leg ulcers subsequent to vena cava ligation; 4 of these have ulcers on both legs. In most instances these ulcers can be healed only temporarily, and then only after prolonged bed rest and supportive treatment. They recur with resumption of routine activities. Three patients have intractable ulcers from chronic venous stasis, which require constant treatment, and which, in spite of intensive therapy, have failed to heal even temporarily. The remaining 15 patients have not had leg ulcers at any time during the period they were followed.

Tenderness on palpation was present in the calf or thigh, or both, in 14 patients. Sixteen had induration in these areas, evidence of persistent venous obstruction, since no concurrent inflammatory process existed.

Prominent venous markings would be expected in the lower extremities following vena cava ligation, since the most adequate collateral channels in these parts are peripheral. These veins, especially the lesser and greater saphenous systems, do not tolerate increased blood flow and volume following such insults as deep thrombophlebitis, superficial femoral vein ligation, or arteriovenous fistula, as is evidenced by the frequent development of multiple varices. Two of the 25 patients had varicose veins prior to operation. Of the remaining, in 16, or 64 per cent, prominent varicosities of the lower extremities developed. In 7 no varices developed but prominent superficial veins were demonstrated.

In 5 patients trophic changes, such as pigmentation, scarring of the skin, and diminished pulses, occurred; in 7 definite spasm of the peripheral arteries was noted.

TABLE II.—FOLLOW-UP OF 25 CASES OF VENA CAVA LIGATION

No. years followed	No. of cases
7	1
6	1
5	11
4	8
3	3
*2	1

*All cases were followed 2 years or more.

TABLE III.—RECORDINGS OF VENOUS PRESSURES AND TESTS EVALUATING ARTERIAL CIRCULATORY EFFICIENCY

Case	Edema	Venous pressure (mm.H_2O)		Isotope removal factor*		Skin temperature	Oscillometric reading
		Right	Left	Right	Left		
F.W.	o	357	220	21	35	Normal	Diminished
L.H.	o	240	245	32	53	Decreased	Diminished
N.K.S.	1+	180	180	23	39	Elevated	Diminished
W.M.U.	1+	260	260	..	..	Elevated	Diminished
J.O.	1+	357	367	49	38	Elevated	Increased
H.M.	1+	385	360	49	40	Elevated	Normal
L.A.H.	1+	170	155	16	40	Decreased	Diminished
L.J.	1+	320	255	9	32	Elevated	Normal
E.M.W.	1+	270	370	23	48	Normal	Diminished
C.G.	1+	267	197	46	56	Elevated	Increased
W.B.	1+	270	240	43	35	Elevated	Increased
J.B.	1+	252	...	45	..	Elevated	Increased
J.C.	2+	252	215	61	73	Elevated	Increased
W.H.	2+	455	380	18	10	Elevated	Increased
B.F.	2+	355	202	56	36	Decreased	Increased
I.T.	4+	340	305	43	26	Decreased	Increased
S.S.	4+	245	255	40	31	Elevated	Diminished
H.D.	4+	257	307	20	24	Elevated	Diminished
C.B.	4+	220	187	41	41	Decreased	Increased
J.A.	4+	315	327	38	24	Normal	Normal
N.S.	4+	260	282	33	43	Elevated	Diminished

*The percentage of radioactive material removed in 10 minutes; normal range is 33 to 45.

The following vascular tests were carried out on 21 of the 22 patients examined (Table III): Venous pressures in the lower extremities were determined with the phlebomanometer by the method of Burch and Winsor. Arterial circulatory efficiency was evaluated by determining the disappearance rate of radioactive sodium as described by Elkin and associates. Oscillometric readings were obtained with the Boulitte instrument, and skin temperature readings with a thermocouple.

Four women complained of menstrual changes, 3 of them having increased flow, and 1, decreased flow. Six remain within the childbearing age or have not undergone hysterectomy; 2 of these employ means of contraception. In the 4 remaining there have been 6 uncomplicated pregnancies and 2 spontaneous abortions. In those patients who did become pregnant, pre-existing edema was aggravated by pregnancy. This data would seem to indicate, as previously reported by Collins and associates, that vena cava ligation per se does not interfere with normal gestation.

Sixteen of the 25 patients evaluated are employed on a full-time basis. Included in this group are several women who do their own housework and have small children. Eight patients are employed on only a part-time basis. One patient is not employable, chiefly because of the sequelae following vena cava ligation. This patient suffers from pain, swelling, edema, trophic changes, severe induration and tenderness of the calves and thighs, intermittent claudication, nocturnal leg cramps, small leg ulcers, eczema, and severe venous stasis. However, in addition to these sequelae, the patient has an intractable gastric ulcer and mild cardiac decompensation.

The 8 patients who are able to work only part time state that they have been forced to limit their activities because of pain, edema, intermittent claudication, easy fatigability, and the recurrence of chronic leg ulcers which developed after vena cava ligation. Several of those employed full time also have difficulties, but with proper care these difficulties are not insurmountable.

All of these patients use one or more of the following measures to reduce disability from their complaints: part-time bed rest, 9; elastic stockings, 9; elevation of legs, 9; ace bandages, 8; mercurial diuretics, 2.

DISCUSSION

Pulmonary infarction is relatively infrequent, but when it does occur it is apt to be catastrophic. The surest known method of preventing embolism from the veins of the lower extremities and pelvis is ligation of the vena cava. As with any procedure, it can be judged only by its total effect: the immediate and the late results. The immediate results have demonstrated the worth of the procedure as a life-saving measure when multiple pulmonary infarctions have taken place. None of the 25 patients evaluated in this study has experienced subsequent pulmonary infarction,

TABLE IV.—COMPARISON OF SEVERITY OF PREOPERATIVE STATUS TO SEQUELAE, USING EDEMA AS THE CRITERION

Case	Phlebitic disease		Edema prior to ligation	Edema at present	No. years followed
	Site or sign	Severity			
S.S.	No known origin	0	0	3–4+	3
J.O.	No known origin	0	0	1+	4
C.B.	No known origin	0	0	4+	5
I.T.	No known origin	0	0	4+	3
J.B.	No known origin	0	0	1+	4
A.G.	No known origin	0	0	1+	5
W.H.	No known origin	0	0	2+	4
L.J.	No known origin	0	0	1+	5
J.A.	No known origin	0	0	4+	4
L.H.	No known origin	0	0	0	4
H.M.	Pelvic phlebitis	0	0	1+	5
W.B.	Calf tenderness	1+	1+	1+	5
W.M.U.	Calf tenderness	1+	0	1+	3
N.K.S.	Calf tenderness	1+	0	1+	5
L.A.H.	Popliteal phlebitis, left	1+	0	1+	4
N.S.	Calf phlebitis, right	1+	0	4+	5
J.C.	Calf phlebitis, right	1+	0	2+	5
C.G.	Femoral phlebitis, right	1+	0	1+	7
M.V.	Calf tenderness; femoral thrombophlebitis, bilateral	2+	0	0	5
F.W.	Femoral and popliteal thrombophlebitis, left	2+	1+	0	5
E.M.W.	Pelvic and right femoral phlebitis	2+	0	1+	2
M.E.	Iliofemoral popliteal phlebitis, bilateral	3+	0	2+	4
M.M.	Pelvic and bilateral femoral tenderness	3+	0	0	4
B.F.	Iliofemoral popliteal phlebitis, bilateral	4+	2–3+	2+	5
H.D.	Postpartum eclampsia; no evidence of phlebitis	?	4+	4+	6

even though 4 of them have since undergone 5 major surgical procedures.

The procedure has produced such dramatic immediate results in seriously ill patients that there appears to be a tendency to extend its indications to the field of prophylaxis. Until long term follow-up studies have delineated the indications for and the most satisfactory results from this procedure, it must be considered to be in a period of evaluation.

In reviewing the literature on this subject, our impression was that frequently some sequelae are overlooked or are not mentioned. The follow-up period in most reports has been months rather than years, which, from our observations, does not allow adequate time for proper evaluation. We have found only 3 reports in which the follow-up studies have covered at least 3 years (2,5,7). Collins reported 59 cases, 5 of which had been followed 6 to 7 years. The composite conclusion of these earlier studies was that circulatory adjustments were adequate and that most patients did not have undue difficulty. No specific study was made of the patients' ability to continue their previous means of livelihood.

TABLE V.—SITE OF ORIGIN OF THROMBOEMBOLISM IN 37 CASES

Site	No. cases	
Iliofemoral and popliteal veins	10	
Popliteal and/or posttibial veins	8	
Pelvic and femoral veins	1	19
Unknown	13	
Prostatic venous plexus	3	
Pelvic veins	2	18

Patients who are to develop postphlebitic or postligation sequelae, or both, usually follow two distinct patterns. A small group will exhibit primarily arteriospastic phenomena, leading perhaps to reflex dystrophies. The large majority will present edema as the most outstanding sequela. It may be transient and subject to control; if it persists, it may initiate the well-known cycle of increased interstitial tissue protein, fibrosis, dermatophytosis, and eventual ulceration.

Edema alone has been the sequela with which most authors have been concerned in the follow-up of their patients. It was the criterion we used in Table IV for comparing the severity of the original illness with postligation sequelae. However, transient edema, per se, has little bearing on the well-being of the patient and his ability to continue his livelihood. More important, we believe, are the presence of arteriospastic phenomena, persistent pain, brawny induration with concurrent dermatoses, and ulceration. These are all prominent and distressing complaints to the patient.

In 1946, Moses concluded that "whenever edema has followed ligation of the vena cava or iliac veins, there has been unequivocal evidence of either persistence or recurrence of the disease process." Our study has failed to verify this. Some of the patients reported herein, with profound venous disease of the lower extremities, have relatively insignificant sequelae following vena cava ligation, while some who were free of disease symptoms in their legs now show profound and incapacitating sequelae in their lower extremities.

Of the 37 patients in whom the vena cava was ligated, only 19 demonstrated evidence of vascular disease in the lower extremity prior to ligation; 5 had venous disease which did not exist in the lower extremities, and 13 had no known or demonstrable site of origin of the thromboembolism (Table V). These latter perhaps represent a group with silent phlebothrombosis. One patient in the latter group developed swelling in the lower extremities less than 6 hours after operation, despite the use of ace bandages, elevation of the legs, and bed rest. Another patient in this group, who developed transient edema following ligation, did well for 3 years and then began having intermittent claudication, easy fatigability of the legs, and mild varicosities, all of which have become increasingly severe in the year prior to this report. There was no other recognizable disease to explain the symptoms and signs present.

In all of the cases observed, there was evidence of the development of collateral venous vessels. However, the fact that these collateral channels developed was no guarantee that untoward sequelae would not appear.

SUMMARY

Reported here are the results of evaluation of 25 patients and the study of hospital records of 37 patients who have undergone ligation of the inferior vena cava during a period of 7 years.

The late sequelae vary from minimal to severe. Only 1 patient in the group of 25 evaluated is entirely free from adverse results. The capacity for carrying out either previous or adequate means of livelihood has been interfered with in 9 patients.

CONCLUSIONS

1. Late sequelae of vena cava ligation cannot be attributed to phlebitic disease alone.

2. The sequelae in the group studied and reported here lead us to conclude that vena cava ligation should be considered only as a life-saving measure, and should not be used for the prophylaxis of thromboembolism.

We believe that this procedure should be held in reserve for the patient who has experienced multiple infarctions, is dangerously ill, and in whom other measures for the treatment of thromboembolism have failed.

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OBSERVATIONS ON WATER DIURESIS AND ON URETERAL PERISTALSIS IN AN INFANT WITH EXSTROPHY OF THE BLADDER

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CONSIDERABLE interest has been aroused in recent years in the water exchanges and renal function of the young. This subject was reviewed at length by McCance (24). The overwhelming body of evidence gathered from histological findings (11, 15, 29), determinations of glomerular filtration rates (4, 25) and renal clearances (35, 45, 47) point to functional immaturity of the kidneys at birth.

Studies of the development of function toward adult levels are few in number. The clearance method has been applied at various ages by West and associates, and by Rubin and Bruck. Earlier investigators (3, 20) studied the rate of elimination of comparable test doses of water by variously aged infants, and showed that there was a gradual increase in the rate at which water was excreted. In a more precise developmental study on dog pups, Adolph was able to show that adult levels were gradually reached, as judged by the half-life of a test dose of 5 per cent of the body weight.

The present investigation was undertaken in order to obtain quantitative information on water diuresis in an infant with complete exstrophy of the bladder and to study the contractions of the ureters during the diuresis. The problem is of more than academic interest in that the question arises of when surgery can best be undertaken with reasonable assurance that the renal function is approaching maturity. This experimental subject was, of course, ideal for such a study since quantitative collections of urine can be made without the possible traumatic intervention of a catheter. Although the anomaly is a rare one [it is said variously to occur once in every 29,000 (41) to once in every 50,000 births (28)] there have been many cases reported in the literature, but few of these have been used in physiological studies. Such subjects have been used by Debenham and associates and more recently by Barnett and associates, in experiments in renal physiology and by Mulder, Slansky, Samschin and Fedorow, in studies on ureteral physiology. Mulder and Fedorow, whose subjects were adults, asserted that there is an increase in the frequency of contraction of the ureters when a copious amount of water is drunk, but this was denied by Samschin and Slansky who studied patients with large vesicovaginal fistulas. The results of the first two investigators have been confirmed by experiments on anesthetized animals (8, 33) and by cystoscopy (30). In fact Alksne stated that "*Man kann wohl sagen, dass dieser Reflex* (the entry of urine into the ureters) *vielleicht als Hauptregulator der Ureterbewegungen erscheint.*"

In this investigation we were also interested in the rate of ureteral contractions and the amount of urine expelled with each contraction at various urine flows. In the course of our work we also had occasion to observe some effects of stimulation of the bladder on urine flow.

CASE REPORT

The patient is a well developed and nourished male infant with complete exstrophy of the bladder who was first seen at the age of 2½ months with a mild fever. A urinary tract infection (Escherichia coli) was found and rapidly cleared during antibiotic therapy. In addition he had an undiagnosed systolic murmur and a hypochromic anemia. He was bottle-fed on whole boiled milk with dextrimaltose, ascorbic acid, and cod liver oil. At the age of 5 months his diet included fruits, vegetables, and cereals.

A retrograde pyelogram at the age of 5 months showed normal structures (Fig. 1) and the urine cul-

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tures showed no growth. The phenolsulfonphthalein excretion estimated colorimetrically at 5 months and at 17 months was 20 per cent and 25 per cent from each kidney in one-half hour.

Blood chemistry studies showed:

	NPN mgm.%	Ca mgm.%	P mgm.%	Na mEq./L.	K mEq./L.	Total Protein %
5 months	45	10.8	4.5			
8 months	44					7.2
17 months	36	11.6	4.0	144	6.4	

He gained weight except during an attack of diarrhea and vomiting at age of 8 months. A full infant diet was instituted when the patient was 10 months old.

Methods. The infant's response to the administration of 3 per cent of the body weight of warmed tap water by stomach tube was tested at various times between the ages of 7 and 12 months. The infant was allowed 200 cubic centimeters of whole boiled cow's milk at 5 a.m. and again at 8 a.m. The studies were started at 10 a.m. The results of the experiment at 7½ months of age confirmed the fact that this regimen does not completely compensate for the loss of body water after a night's fast since most of the water of the milk is required to eliminate the metabolic products due to the ingestion of the milk. In subsequent experiments water was supplied to the baby *ad libitum* in addition to the milk for at least 1 hour prior to the administration of the test dose. The importance of precautions to insure water balance during studies of diuresis cannot be overemphasized.

The experiments were carried out at a room temperature of 28 to 29 degrees C. The infant was weighed to the nearest 5 grams at quarter to half-hour intervals. Neither diarrhea nor vomiting was encountered during the course of the experiments.

In order to avoid irritation and possible trauma, catheterization was not performed. Instead, in order to determine the volume flow of urine, a piece of sterile gauze which had been previously weighed and kept in a glass-stoppered weighing bottle was placed at the ureteral orifices for a period of 2 to 5 minutes so as to imbibe the urine which issued forth during this period. At times the gauze was left in place, while at other times when it was desired to count the rate of contractions of the ureters simultaneously, the gauze would be used to wipe the orifices free of urine at each contraction. This latter procedure was found necessary in order to clear the field. The flow was calculated on the basis of surface area estimated from the nomogram of Hannon (27). At frequent intervals urine for analysis was collected and placed in small cork-stoppered test tubes which were paraffined and placed in a cold room at 4 degrees C. Analyses for chloride by the microelectrometric titration method (23) and for total solids estimated from the refractive index at 20 degrees C. were performed within a day.

RESULTS

Diuresis. The urine flow per minute per square meter of body surface at 1 year of age is plotted against the time in hours after the administration of the loading dose of 3 per cent of the body weight in graph 1A. Each point on the curve near the maximum (from 1 to 2 hours) represents the average of two successive periods of observation calculated from the data of graph 1B. It will be noted that the onset of diuresis is rapid and reached a maximum within an hour and a half. There are also marked changes in urine chloride concentration and in the refractive index difference, i.e., the difference in the scale readings of the dipping refractometer between the urine sample and distilled water; these changes inversely parallel the diuresis curve (graph 1C). For purposes of comparison, the average rate of urine output of adults calculated from the data of Adolph, assuming a body surface of 1.73 square meters, has been plotted in graph 1A. The maximal rate observed in this infant at one year of age is considerably higher than these values, and higher, in fact, than any rate reported for normal human adults.

Inhibition of diuresis. In a previous observation period on the infant at 10 months of age, marked fluctuations in urine flow at the time of maximum diuresis were seen. The question arose whether these were normal fluctuations perhaps characteristic of diuresis at this age or whether they arose as the result of some part of the procedure we had employed. It was noted that stimulation of the bladder mucosa, as when the area was wiped free of urine, proved irritating to the baby. It was decided, therefore, to compare the rate of urine flow when the bladder was deliberately stimulated by applying a moderate, but constant digital pressure during the collection period with the rate of flow when no stimulation was applied. The results of this experiment are recorded in graph 1B which represents the rate of urine flow during the course of a diuresis induced at 12 months of age. The circles represent the rate of flow when deliberate pressure is applied to the surface of the bladder. This procedure often provoked crying in the baby. It can readily be

seen that stimulation of the bladder by this means resulted in a marked fall in the rate of urine flow both on the ascending and descending sides of the diuresis curve.

Contractions of the ureters. It is evident from graph 2 that the frequency of contraction of the ureters and the average volume of urine expelled by each contraction parallel the diuresis. These two quantities must therefore be directly related to the minute volume of urine, as is seen in graph 3. The general impression of an increase in the amplitude of the contractions was obtained by direct observation, for large high spurts of urine were seen during the diuresis.

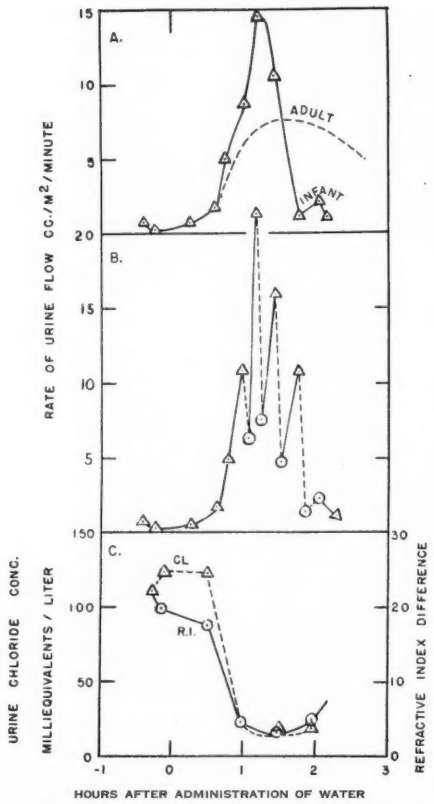
The contractions of the two ureters were almost always asynchronous; only in rare instances were they simultaneous. It was sometimes observed that while moderate activity was exhibited on one side (about 2 contractions per minute), there might be almost no activity on the other side where a single contraction might be followed by 5 minute quiescence. However, this was seen only at very low rates of urine flow. After water was administered, both ureters were brought into increased activity, and the rate of contraction of the hitherto quiescent ureter might at times exceed that of the previously more active one. While at any one time there might be a difference of activity between the two ureters, it was not observed that one ureter was consistently more active than the other.

Fig. 1. Retrograde pyelogram taken at 5 months of age. Note absence of the symphysis pubis.

DISCUSSION

The concept of development of the individual implies progressive changes leading toward a more or less definite anatomic and physiological status. The point at which mature status is reached varies with the organ or function under consideration. In dealing with one of the most important processes of the body, the regulation of the internal environment, we find that the organism is so adjusted as to protect itself against water excesses or deficits within certain physiological ranges (1). It is apparent that the newborn of those mammalian species thus far tested is less able than the adult to maintain a constant internal environment and are thus more vulnerable to marked changes in the constitution of their body fluids. Adolph, in work on young dog pups, showed that the plasma remains diluted for several hours after the administration of water. A 24 hour deprivation of food and water produced in the newborn rat marked hemoconcentration, an increase of plasma urea and a loss of muscle water, whereas in the adult, these did not change significantly (18). Hypertonic sodium chloride or urea solutions are retained for much longer periods by human infants, and produce more prolonged elevations of these substances in the plasma, than is the case in adults (9) and it is found that there is but a relatively small rise in the urine excretion of the administered solids. This is consistent with the findings of marked urinary hypotonicity in infancy (17, 25).

Since differences are found between newborn and adult, the question arises when and how is maturity attained. The available in-



Graph 1. Diuresis at 1 year of age in response to 3 per cent of body weight by stomach. A, The urine flow on basis of surface area for the infant and the average values for the adult. B, The inhibition of urine flow when digital pressure is applied to the bladder (at circles). C, The urine chloride concentration and refractive index difference.

formation pertinent to this problem is still fragmentary. West and associates find that the glomerular filtration rates corrected for body surface area may reach adult levels in man as early as 10 to 20 weeks and the renal plasma flow as early as the thirtieth week, while Rubin and associates indicate that these values rise slowly during the first year and reach adult levels sometime between the first and second years of life. Urea clearances have been shown to approach the adult level by the end of the first year (47).

These studies have emphasized the comparative renal immaturity of infancy. It should be pointed out that "osmotic regulation" involves a multitude of factors both renal and extrarenal. Mention need be made only of the current ideas relating to the role of some of the endocrine organs (14, 44) in water and electrolyte metabolism. It matters little from an operational standpoint of the organism that its kidneys are mature, but other factors which may be brought to bear on the kidneys less mature, or vice versa, so that the net effect is still an incomplete adult response to a water load. It is important, therefore, to study the response as a whole as well as its constituent parts in order to arrive at some idea of their relation to the organism's economy.

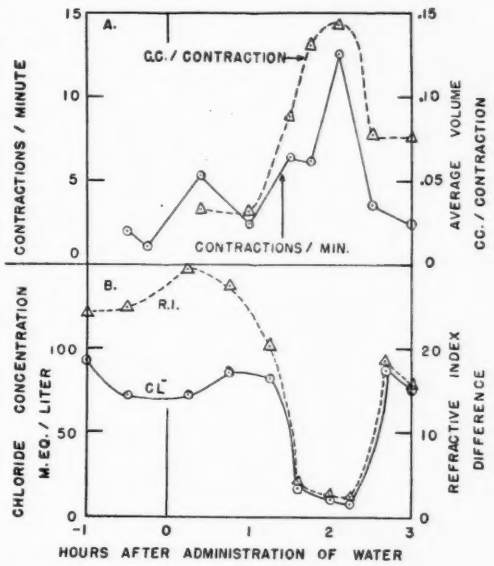
There have been very few studies on water diuresis in human infants. The work of Aschenheim and Lasch first drew attention to the slow elimination of a test dose of water in children under 3 months of age, and showed a subsequent gradual increase so that by the end of the first year the administered water is completely eliminated by the renal route at the end of four hours. It is somewhat difficult to draw any accurate comparisons with water diuresis in adults (1, 32, 43), since Aschenheim and Lasch did not calculate their results on the basis of body weight or surface area, and depended on spontaneous micturitions and readings taken at hourly intervals.

Some of these objections have been overcome in the results reported in this paper. It seems evident that a full diuretic response to the ingestion of a large amount of water is developed in this infant at least by the end of the first year. This diuresis is characterized by a rapid onset beginning within half an hour and reaching a maximum by one and one-half hours, so that at the end of this time one-half of the test dose has been eliminated through the kidneys (graph 1A). Water diuresis in man per unit of weight or of surface is slower than in many other mammalian species (1). The rate of water elimination observed in the infant under study at 1 year is considerably higher than the average values reported for man and higher than values obtained by earlier investigators, if one assumes any reasonable figures for body weight or surface area. It is entirely possible that diuresis

in infants of 1 year of age or older may exceed that of adults, but information in the literature is lacking for all other species as well as for man.

It should be particularly noted that the yearling infant is able markedly to dilute its urine to a chloride ion concentration of 10 milliequivalents per liter and to an extremely low refractive index (graph 1C). There is no significant difference in the urine concentration during diuresis in the infant at 10 months and at 1 year of age.

Another point to be considered is that the rate of physiological development may vary among individuals, so that a more complete study is indicated. Indeed, in view of the paucity of information on diuresis in infancy, it is one of the purposes of this paper to present the partial data obtained in the hope of stimulating interest in this subject.

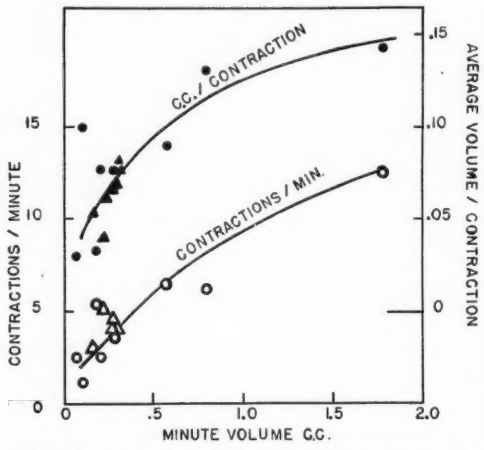


Graph 2. A, Ureteral activity at 10 months of age after water administration; the frequency of peristalsis and the average volume of urine expelled by each contraction. B, The urine chloride concentration and refractive index difference.

CONTRACTIONS OF THE URETERS

The ureter has been shown to be not a passive tube through which urine courses, but an active organ in excretion as a result of its contractions (12). There has been considerable research and much speculation on the origin of the contractions of the ureters. The independence of ureteral contractions from the central nervous system has been amply demonstrated by studies on the isolated ureter (21, 37, 40, 42). There has been considerable controversy as to the distribution of the autonomic nervous supply to the ureters, but the presence of intrinsic ganglia is well established (2, 22, 33), and study of peristaltic activity of the ureters has centered around its myogenic or neurogenic origin. The idea of a myogenic origin was held by Engelmann on the basis of the histological structure of the smooth muscle of the ureters and the response to stimulation. Protopopow, on the other hand, attributed the increase in ureteral activity with increased urine flow to nervous stimulation caused by the entrance of urine into the lumen. Stimulation of the hypogastric nerve has been reported to enhance ureteral movements (42). More recently evidence has been adduced in support of the idea of a myogenic origin. Lapides, in an investigation of the physiology of the intact human ureter in unanesthetized subjects by the use of pharmacological agents thought to block the autonomic nervous system (tetraethylammonium ion) or to simulate the effects of stimulation of the autonomics, finds that the change in ureteral activity is due entirely to the effects of these drugs on urine output and cannot be attributed to any direct effects of the drugs on the ureters. The conclusion is drawn that ureteral activity is governed mainly by the flow of urine which exerts a stretch on the smooth muscle fibers of the ureter. Additional evidence for the myogenic theory comes as the result of the work of Bozler who studied the action potentials produced by sudden distention of ureteral muscle. An increase in pressure above threshold yielded a slow local response which varied with the force applied, and if sufficiently large produced a conducted, all-or-none response.

The dependence in infants of ureteral peristalsis on flow of urine is well borne out in our experiments. The rates of contraction are the same as those reported for adults at com-



Graph 3. Ureteral activity and urine flow at 10 months of age.

parable minute volumes (13, 19). The rate of peristalsis and the average volume of urine expelled at each contraction, which reflects, no doubt, the amplitude of contraction, parallel the diuresis curve (graph 2A). Although there is a large increase in these values at high urine flow, the changes are somewhat lower than one might be led to expect on the basis of the slope of the curves at low urine flow. Or, an increase in urine output at low flow produces variable changes in frequency and amplitude, while at high flow both frequency and amplitude tend to change more consistently in the same direction so that an increase in total activity is effected, without an increase in ureteral back pressure which would tend to decrease urine formation.

EFFECTS OF BLADDER STIMULATION ON URINE FLOW

Diuresis was inhibited during the period of stimulation of the bladder evoked by applying moderate pressure on the exposed posterior wall (graph 1B). It is possible that pain fibers are present since the baby could be made to cry by this procedure. The question arises, of whether we are dealing with a nonspecific pain stimulus or a possible vesicorenal reflex. In a study of the effect of pain produced by pressure applied to the head on renal function, Wolf finds that both the inulin and diodrast clearances are reduced with a resultant decrease in urine flow and an increase in filtration fraction, suggestive of renal vasoconstriction. The urine output remained low for an extended period after the withdrawal of the pain stimulus, which might make one question whether a similar mechanism applies in the case here under discussion. It should be pointed out, however, that the procedures are not entirely comparable in that both the duration and the intensity of the pain stimulus applied are considerably less and the rate of urine output much higher in the infant. It seems probable that the inhibition of diuresis cannot be explained on the basis of a release of the posterior pituitary antidiuretic hormone since the effects observed are of short duration (44).

A decrease of urine flow under the conditions of the experiment can be due either to a fall in kidney output or to an inhibition of ureteral peristalsis, or both. If the postulate of Lapides is correct, that the ureter is an autonomous organ whose activity is influenced by the rate of urine flow, then we can eliminate the latter possibility. However, other investigators (8, 30) brought forth evidence to show that distention of the bladder produced an increase in the frequency of contraction of the lower portions of the ureters in anesthetized and unanesthetized dogs, which could not be attributed to a vesicoureteral reflux. Unfortunately, we have no observations on the rate of contraction of the infant's ureters during the period of inhibition. We can only assume, on the basis of the work of other investigators, that there was either no direct effect on the ureters by bladder stimulation or more doubtfully an increase in activity.

A decrease in urine output upon filling of the bladder with fluid has been observed by Pflaumer and Pico and a similar decrease in urine flow upon electrical stimulation of the bladder to contract by Sérès and Boeminghaus. Pflaumer noted particularly the seemingly rapid shift of urine flow by markedly changing the volume of fluid in the bladder and attributed the changes to a vesicorenal reflex. Of course, in this case of exstrophy, there can be no question of distention of the bladder and the results of some of these other investigators

have bearing only in that they represent sensory stimulation. It might also be questioned whether an atrophic bladder or a bladder mucosa exposed to the air has a normal sensory innervation.

It seems most probable that the inhibition of diuresis which we have observed is due to an inhibition of urine production, perhaps through renal vasomotor reflexes, although we are not certain of the mechanism involved.

SUMMARY

1. Water diuresis has been studied in an infant with complete exstrophy of the urinary bladder and has been found to reach adult levels by the end of the first year of life.

2. Rates of urine flow in this infant at 1 year of age exceed those reported for adult man, when the values are compared on the basis of surface area or body weight. The possibility is suggested that infants at this stage of development may normally have higher rates of output than adults. Further investigation is indicated.

3. An increase in urine flow produces an increase in the frequency and amplitude of ureteral contractions. The maximum frequency of contractions observed was 12 per second.

4. Bladder stimulation by the application of digital pressure results in an inhibition of diuresis, the mechanism of which deserves further inquiry.

5. From these data it seems reasonable to conclude that surgery designed to correct the exstrophy might be performed about the age of 1 year, provided there are no other contraindications.

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TECHNIQUE FOR AORTIC EMBOLECTOMY

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IN the removal of an embolic occlusion of the abdominal aorta, many and varied techniques have been described. Through the process of trial and error a technique for aortic embolectomy was evolved which is herein presented. The technique is based on experience obtained in operating upon 8 patients, in each of whom there was a "saddle" occlusion of the abdominal aorta. In the removal of emboli from arteries other than the abdominal aorta, the same technique is employed.

TECHNIQUE

A left paramedian muscle retracting (lateral) incision is employed (Fig. 1A). The incision extends approximately one-third above and two-thirds below the level of the umbilicus. After the peritoneal cavity is entered the patient is placed in the Trendelenburg position. The small intestines are displaced upward and are maintained in position by suitably placed moist gauze pads. A linear incision is made through the posterior parietal peritoneum overlying the lower portion of the abdominal aorta and its bifurcation. The surrounding fatty areolar tissue is separated by blunt dissection and the occluded segment of the aorta is exposed. By digital palpation the extent of the thrombus, proximally in the aorta and distally in the iliac arteries, is determined. The adventitia layer is removed from the anterior surface of the distal 4 to 5 centimeters of the abdominal aorta. Employing the left index finger,[1] the first assistant gently compresses the aorta immediately proximal to the thrombus (Fig. 1B). A linear incision approximately 3 centimeters in length is made through the anterior wall of the aorta overlying the middle portion of the contained thrombus. This permits the thrombus to extrude partially through the incision (Fig. 1B). A series of interrupted everting mattress sutures of No. 00000 silk (Deknatel) swaged on a small curved needle are inserted. The silk suture strands that overlie the herniated segment of the thrombus are separated into two divisions and are retracted on nerve hooks both proximally and distally, respectively (Fig. 2). By digital compression the distal portion of the thrombus, first in one and then in the other common iliac artery, is "milked" upward and extruded through the incision in the aorta (Fig. 2). Subsequent to this maneuver and provided an early operation is performed, free retrograde bleeding usually occurs. This bleeding indicates patency of the collateral vascular channels below the site of the aortic occlusion; a favorable prognostic sign. Next, the common iliac arteries are occluded with digital compression immediately distal to the bifurcation of the aorta by the right hand of the assistant or the left hand of the surgeon, and the compression of the aorta proximal to the thrombus is slowly released (Fig. 3). The arterial pressure in the aorta generally is sufficient to expel forcibly the remaining portion of the thrombus through the aortic incision. If not, the thrombus may be evacuated by "milking" it downward by gentle digital compression. The digital occlusion of the common iliac arteries prevents the dissemination of thrombotic emboli into the peripheral arteries. The discharge of the thrombus is followed by a forceful pulsatile flow of blood that is stopped by the compression of the aorta proximally by means of either the index finger (Fig. 4) or an anatomical tissue forceps. The operative field is cleansed by irrigation with sterile saline solution which is removed by suction. The silk everting mattress sutures previously inserted are drawn taut, the compression of the aorta is released, and the sutures are tied (Fig. 5). If sites of bleeding should persist, hemostasis is obtained either by gentle compression of the suture line

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[1] If for technical reasons, the use of the index finger proves unsatisfactory, a 10 inch length anatomical tissue forceps may be conveniently substituted.

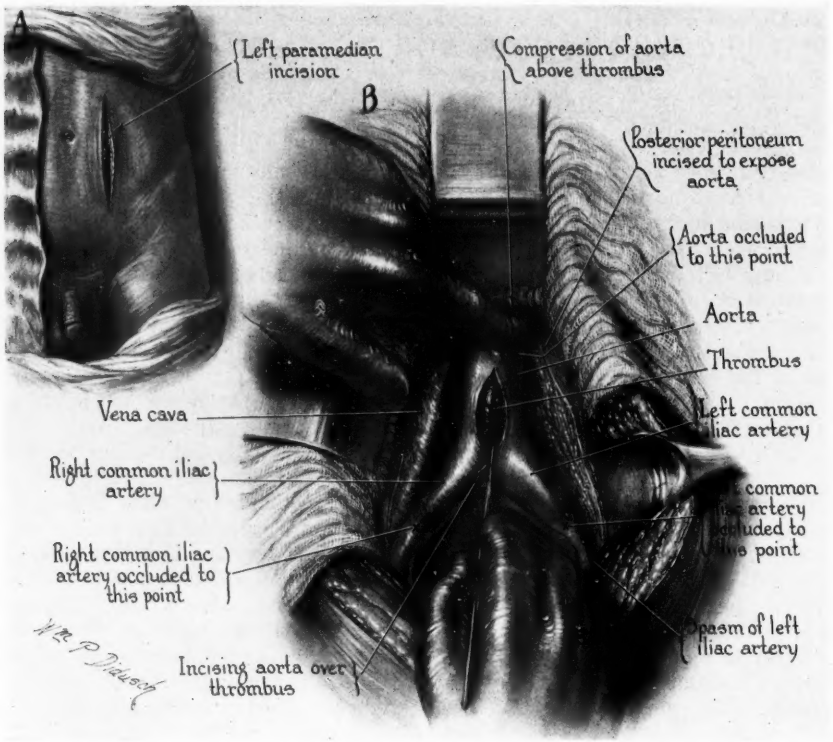

Fig. 1. A, The incision employed, a left paramedian, is depicted. B, The lumen of the aorta is occluded by digital compression and the anterior wall of the aorta overlying the contained thrombus is incised. The thrombus which extends distally into both common iliac arteries is herniated partially through the incision. The left common iliac artery distal to the thrombus is in spasm.

for several minutes by means of a sterile gauze sponge or by the insertion of additional interrupted silk sutures, dependent upon the severity of the hemorrhage.

Five cubic centimeters (50 mgm.) of heparin is injected into the lumen of the aorta proximal to the arteriotomy and maintained in situ for 1 minute by digital compression of the aorta both above and below the site of incision. The incised portion of the posterior parietal peritoneum is not sutured. A layer closure of the wound is performed, interrupted silk sutures being used. Drainage of the wound is not employed. Because of the high incidence of complications due to hemorrhage, anticoagulant therapy postoperatively has been discontinued.

DISCUSSION

The surgical approach to the lower portion of the aorta and its bifurcation may be extraperitoneal, transperitoneal, or retrograde. The transperitoneal approach, spinal anesthesia being used, is preferred. Although objected to by many, its advantages are believed to exceed the proclaimed disadvantages.

The basic principles that are believed to underlie the successful surgical removal of an arterial embolus are: (1) an early operation, preferably within the first 8 hours; (2) an adequate surgical exposure; (3) the production of a minimum of trauma, particularly to the intima; (4) the interruption of the circulation for a minimum period after the thrombus is removed.

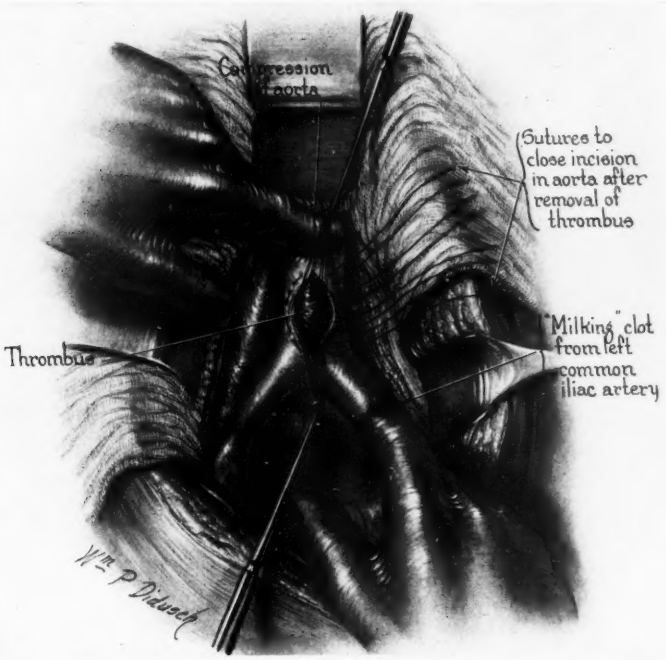

Fig. 2. Digital compression of the aorta is maintained proximal to the thrombus and the silk suture strands are retracted on nerve hooks to permit the free escape of blood clots. The thrombus, first in one, then in the other common iliac artery, is "milked" upward through the opening in the aorta.

In most of the surgical techniques commonly employed for aortic embolectomy, mechanical devices or tape ligatures are used to occlude the aorta proximal to the blockage and the common iliac arteries distally. In the majority of patients with a "saddle" occlusion of the abdominal aorta, varying degrees of atherosclerosis are present. The degenerative changes occur predominantly in the posterior and lateral walls of the aorta. The occlusion of the lumen of the aorta by a mechanical device, a traction tape ligature, or an occluding tape ligature may produce a fracture of an atherosclerotic plaque and an injury to the intima. This predisposes to the formation of a local thrombus. In general, the use of such methods for hemostasis requires the complete mobilization of the distal portion of the abdominal aorta and its bifurcation. A notable exception is the technique described by Linton. This mobilization of the aorta prolongs the operation, risks the danger of dislodging a portion of the thrombus to form an embolus and increases the likelihood of troublesome hemorrhage.

In the technique herein described, mechanical devices or tape ligatures for hemostasis are not used. Instead, for this purpose, the left index finger of the assistant or an anatomical tissue forceps 10 inches in length is employed. Protective rubber shods predispose to slipping of the forceps off the walls of the aorta and are not used. The use of the index finger or tissue forceps produces a minimum of trauma, does not require the mobilization of the aorta and permits the immediate release or application of a compression force to the aorta; a desired technical aid. Furthermore, a delicate adjustment of the compression force applied may be obtained.

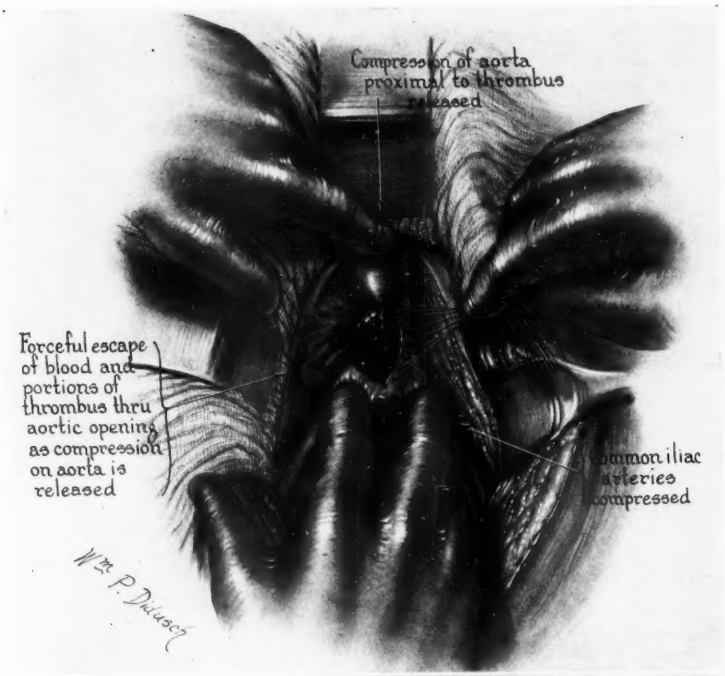
Compression of aorta proximal to thrombus released
Forceful escape of blood and portions of thrombus thru aortic opening as compression on aorta is released
Common iliac arteries compressed
Wm. P. Dalusch

Fig. 3. To prevent the peripheral dissemination of emboli the common iliac arteries are occluded digitally and the compression of the aorta proximal to the thrombus is released. The force of the aortic pulsations ejects the clots of blood through the incision. This is followed by active pulsatile hemorrhage, the control of which is being initiated by traction on the silk suture strands.

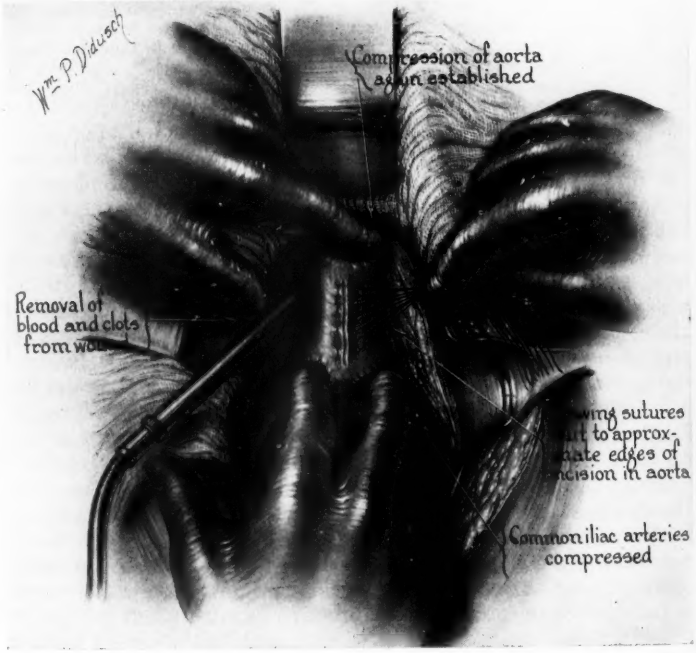

Fig. 4. After complete evacuation of the thrombus, the lumen of the aorta is momentarily occluded proximal to the incision and the suture strands of silk are drawn taut to close the opening in the aorta. The operative area is toiletted by irrigation with saline solution that is removed by suction siphonage.

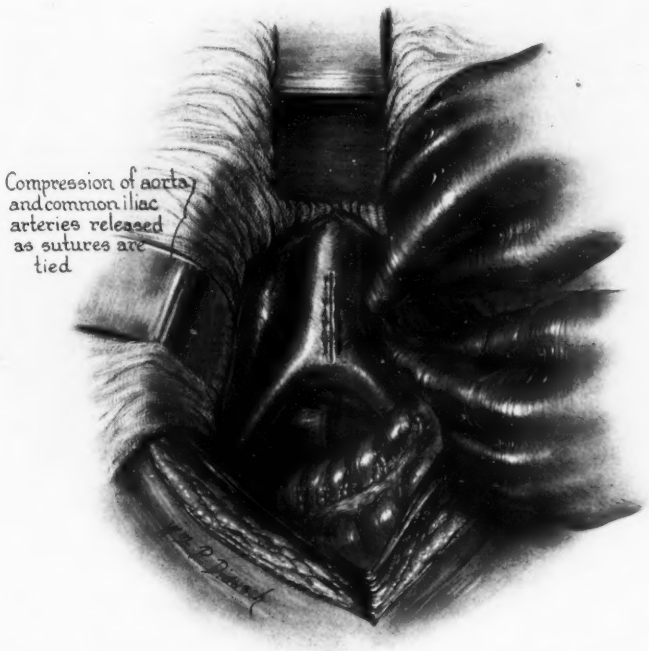

Fig. 5. The compression of the aorta and the common iliac arteries is released and the occluding traction sutures of silk are tied.

Before doing the aortotomy, the lumen of the aorta is occluded proximal to the thrombus. Otherwise, the force of the aortic pulsations would expel the thrombus through the incision in the aorta and produce excessive hemorrhage. Following the aortotomy, the thrombus herniates partially through the incision. This herniation of the thrombus produces an eversion of the incised margins of the intima and facilitates a meticulous insertion of the everting mattress sutures of fine silk. After the thrombus is evacuated, traction upon the previously inserted sutures closes the incision in the aorta and controls hemorrhage. Accordingly, proximal occlusion of the aortic lumen and interruption of the circulation is only momentary while the sutures are drawn taut. Contrariwise, in techniques wherein the sutures are inserted after the thrombus is removed, proximal occlusion of the aorta and interruption of the circulation for a prolonged period are an absolute necessity. In the experience of the author such techniques predispose to a high incidence of local recurrent thrombosis. Instrumentation of the lumen of the aorta for the removal of a thrombus may cause an injury to the intima and it is judiciously avoided. It is considered both unnecessary and unwarranted.

In the performance of aortic embolectomy severe arterial spasm of one (Fig. 1B) or both common iliac arteries has been repeatedly observed. This spasm was present even though a satisfactory spinal anesthesia was in effect. Furthermore, the periarterial injection of procaine (2 per cent) beneath the adventitia of the involved artery did not relieve the arterial spasm. However, after removal of the thrombus the spasm was relieved. On the basis of these observations the performance of a complementary lumbar sympathetic ganglionectomy or supplementary procaine (2 per

cent) "blocks", or both, of the lumbar sympathetic ganglia was discontinued. In addition, anticoagulant therapy postoperatively was stopped. This was considered advisable because of the high incidence of complication due to hemorrhage. Following the establishment of this routine, one that is contrary to established opinion, experiences to date have proved satisfactory.

In any prescribed technique for arterial embolectomy it is believed essential that the four basic principles previously described be adhered to if increasingly satisfactory results are to be obtained.

SUMMARY

The basic principles underlying the successful surgical removal of an arterial embolus are: (1) an early operation, preferably within the first 8 hours; (2) an adequate surgical exposure; (3) the production of a minimum of trauma, particularly to the intima; (4) the interruption of the circulation for a minimum period after the thrombus is removed. A technique for aortic embolectomy embodying these principles is described.

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A SPLIT T TUBE AND A RETAINING APPARATUS FOR INDWELLING T TUBES IN THE REPAIR OF STRICTURES OF THE BILE DUCT

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WHILE the split tube was mentioned and illustrated in a recent article[1] discussing strictures of the bile duct, which appeared in SURGERY, GYNECOLOGY AND OBSTETRICS, it seems worth while to describe in more detail the method of using the tube. In the long article mentioned opportunity did not present itself to describe what I sought to attain in devising this tube; therefore, because the apparatus may prove useful to others who may have to deal with strictures high in the hepatic duct close to the point of division of the duct into the right and left hepatic branches, it is described here.

The number of patients operated upon at the clinic for strictures of the bile duct is now 314. Many of these patients, who had had numerous operations before they came to the clinic for further surgical treatment, had lost so much of their hepatic ducts that there remained only a short cuff (Fig. 1) of the common hepatic duct or of the two separated ends of the left and right hepatic ducts, the common hepatic duct having been completely removed.

In the diagrammatic illustration (Fig. 2) is shown the plan of repair, devised by Richard B. Cattell of this clinic, by direct end-to-end anastomosis after mobilization of the common duct out of the head of the pancreas with either the short stump of the hepatic duct or the two hepatic ducts approximated (Fig. 3, a

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[1] LAHEY, F. H., and PRYTEK, L. J. Experience with the operative management of 280 strictures of the bile ducts, with a description of a new method and a complete follow-up study of the end results in 229 cases. Surg. Gyn. Obst., 1950, 91: 25–56.

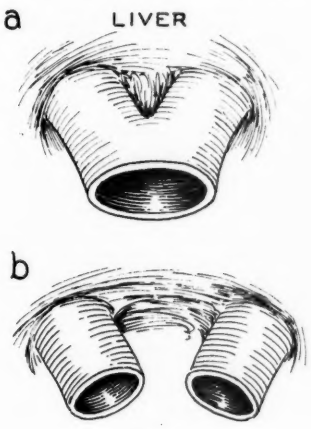
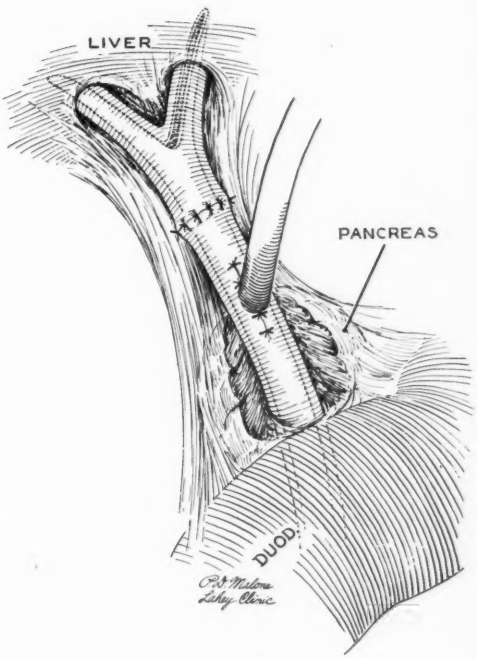


Fig. 1.



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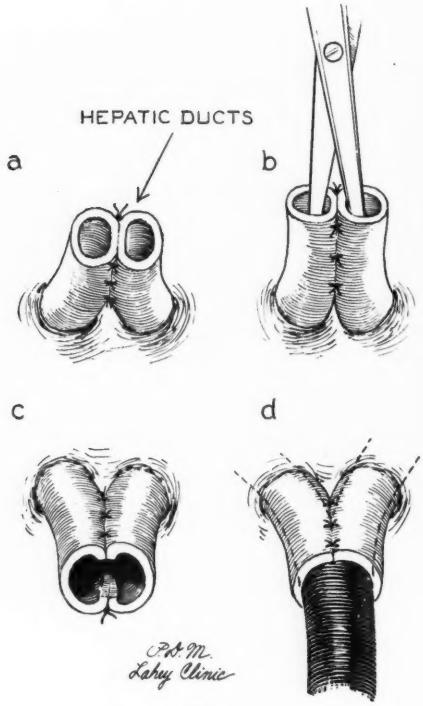

Fig. 3.

and b), and with the septum cut to convert them into one duct (Fig. 3, c and d). In Figure 4 is shown such an improvised T tube with one end split and in place.

Until the tube described was developed, it had been necessary for us to employ a make-

Fig. 4.

shift type of divided T tube by cutting the upper end of a T tube, front and back, so that it could be divided into two half limbs (Fig. 5). An attempt was then made to introduce one-half of the divided tube into the left intrahepatic duct and the other half into the right intrahepatic duct.

It is impossible to pass a T tube of a desirable caliber with the upper end having two complete limbs through the usual sized common hepatic duct, since the caliber of the

Fig. 5.

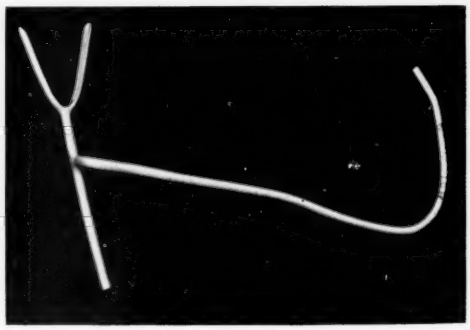

Fig. 6.

hepatic duct is not great enough to take two tubes of adequate caliber. For this reason, I have had made a tube of the type shown in Figure 6. This is a T tube with flared upper ends, the walls of each end consisting of a little more than half of a tube and so constructed that, when held together, the caliber of both ends equals but the caliber of a single tube. A flare in the end of each half tube automatically spreads the tubes open into their proper position in the right and left hepatic ducts when it is introduced through a short common hepatic duct. The tube serves as a collector of bile from either duct, directing the flow of bile into the central aperture of the tube. As the divided ends automatically flare open upon the introduction of one end into the left intrahepatic duct and the other into the right, a central aperture to collect the bile for discharge into the main tube to be carried into the duodenum or jejunum can be obtained; the open flaring of the split ends automatically directs one end into the right and the other end into the left intrahepatic duct.

It is important that the lower end of the T tube be sufficiently long that it can be passed through the sphincter into the duodenum and the upper end of the tube sufficiently short that by shortening it or leaving the divided end of the tube long, as shown in Figure 6, the flared ends of the tube can be introduced to a proper length intrahepatically within the right and left hepatic ducts.

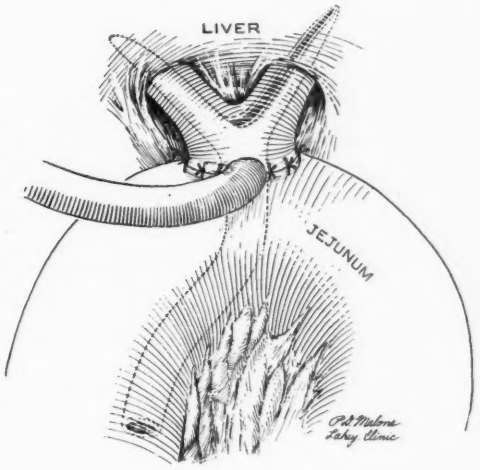

Fig. 7.

This divided tube is of value not only in the direct end-to-end anastomosis of common to hepatic bile ducts, when it can be done, but it is likewise of value to maintain patency of a hepaticojejunostomy and a hepaticoduodenostomy when end-to-end anastomosis is not possible and when such a short stump of hepatic duct remains that the introduction of a T tube with but a single end would result in its being placed only in the right or left portion of the divided hepatic ducts (Fig. 7). In such instances good drainage from both lobes of the liver would not be obtained.

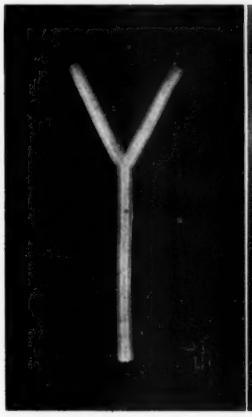

Fig. 8.

Fig. 9.

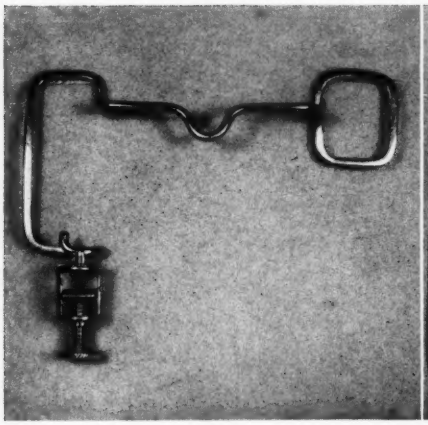

Fig. 10.

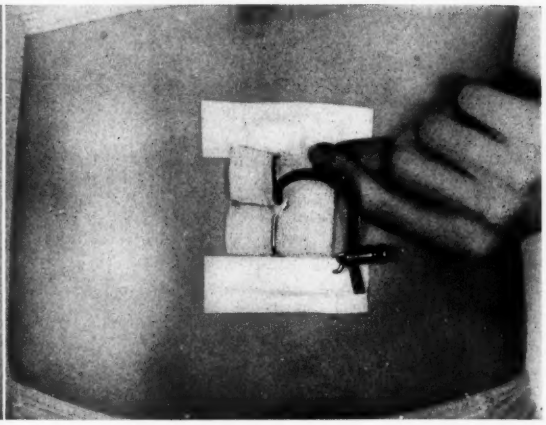

Fig. 11.

We have frequently employed Y tubes of the bouncing clay variety, as shown in Figure 8. The roentgenogram (Fig. 9) shows such a tube which has been in place for 19 months, with no complications. There are, however, certain advantages in the plan of maintaining by means of a T tube, patency, of a hepaticojejunostomy or of a hepaticoduodenostomy anastomosis, used as a last resort. The advantages are that the tube can be irrigated morning and night and can be left in place for a year or more until good patency within the anastomosis and the ducts has been established.

This tube is not presented with the idea that it will solve all of the difficulties encountered in dealing with strictures of the bile ducts but solely as a plan to provide a means of drainage in those complicated cases of high strictures in which one limb of the T tube must be placed in the right hepatic duct and the other in the left hepatic duct intrahepatically.

RETAINING APPARATUS

The little apparatus shown in Figure 10 was devised for us by a former patient, who wore such a T tube for a long time. It is an aid in maintaining the T tube in place conveniently. It also insures against the tube being accidentally withdrawn and at the same time makes it possible for the patient to take a bath, with the tube in place. The tube has been found to be a particularly useful apparatus for patients with strictures of the bile duct who must frequently wear a T tube for a year or more.

It is to be noted in Figure 11 that the wire frame is strapped to the abdomen with waterproof adhesive, and the tube is strapped to the small bent portion of the transverse rod on the frame also with waterproof adhesive. It may also be noted that on the end of the tube is a screw clamp and on the end of the wire frame a small claw to which the screw clamp can be threaded so that the tube can be shut off, maintained in place, and no objectionable projection appear beneath the clothes.

We now have several patients wearing this apparatus with great satisfaction. It is not required to change the apparatus oftener than once in several weeks.

A NEW METHOD OF TREATMENT OF TRICHOMONAS VAGINALIS VAGINITIS

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WHILE Donne in 1836, described Trichomonas vaginalis in certain women with leucorrhea, it was not until 1916 that Hoehne suggested that this protozoan organism might be of pathogenic significance. In 1940, Trussell and Plass definitely established that Trichomonas vaginalis can produce the clinical syndrome of Trichomonas vaginalis vaginitis. These investigators were able to induce the disease in 9 uninfected women by inoculation with a bacteria free culture. This work was later confirmed by Hesseltine.

Despite this definite evidence of pathogenicity, the actual role of Trichomonas vaginalis remained obscure; for it is generally believed that many who harbor this parasite are essentially unaffected by it. Indeed, Cornell and his associates found 47 to 87 per cent of cases of Trichomonas vaginalis vaginitis to be asymptomatic; though Johnson and Mayne reported that 75 per cent of their patients were symptomatic. It is our opinion that the mental attitude and social training of the patient may be an important factor in determining the presence and severity of the symptoms. In a series of 63 of our cases, only 49 of them had complaints, yet definite objective evidence of an inflammatory reaction was noted in all but 6 patients. There appears to be a marked variation in the threshold of discomfort in women. Again, it was often our experience that after evidence of infection was called to the attention of the patient, she would admit the existence of symptoms. It is quite difficult to evaluate the ramifications of "modesty."

The mere presence of Trichomonas vaginalis does not necessarily establish it as the fundamental pathogenic agent. In many instances, bacteria may be the primary etiologic factor with trichomonads playing a secondary role. There have been diverse views as to the potential seriousness of Trichomonas vaginalis vaginitis. Some have maintained that it increases puerperal morbidity (4), while others have denied this (24). Hees reported that this protozoan organism had been demonstrated by culture and smear in the blood stream, endometrium, chronically inflamed tubes, ovarian cysts, and peritoneum. Also, he stated that pelvic abscess caused by this organism is not rare. At present, however, it is generally believed that this infection is unlikely to produce serious effects (8).

Perhaps the greatest source of confusion is the lack of adequate knowledge concerning the epidemiology of Trichomonas vaginalis vaginitis. It is known that this infection is more common in the lower economic and social strata. Likewise, it is more prevalent and more likely to recur after treatment in those who have poor standards of personal hygiene. The importance of male infestation as a source of infection in Trichomonas vaginalis vaginitis has recently been emphasized (11). It has been reported that 25 to 80 per cent of the husbands of infected women harbor these organisms (10, 19), and Allison believes that trichomoniasis should be regarded as the seventh venereal disease. Recently, we successfully treated 10 cases of male trichomoniasis with oral aureomycin (20). Other suggested sources of infection are contaminated bed-pans, douche bags, bath tubs, pools, toilets, or linens. Hesseltine considers the lower urinary tract to be a source of infection (1, 15). Bland and Rakoff do not believe that the rectum and mouth are frequent sources of infection. The glands of Skene and Bartholin may harbor Trichomonas vaginalis and cause recurrence (26).

With so much uncertainty concerning the pathogenesis and epidemiology of this infec-

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tion, its treatment has naturally remained confused. In 1943, the Council on Pharmacy and Chemistry of the American Medical Association felt required to publish an editorial in the *Journal of the American Medical Association* on "The Status of Treatment of Vaginitis Associated with Trichomonas Vaginalis" (8). It was explained that this report was released because of the extreme confusion manifested in many letters from physicians received by the Council. This group reviewed the treatment of Trichomonas vaginalis vaginitis and found that the duration of treatment ranged from 2 weeks to 1 year and that the criteria for cure were freedom from symptoms and parasites for periods ranging from 2 to 24 months. Likewise, it was discovered that 90 substances were being employed in treatment. Most therapeutic methods were prolonged, messy, and utilized multiple substances (up to 7) in combination or in sequence. The occurrence of toxic reactions to many of these preparations was noted, and the importance of an essentially harmless agent was stressed. There are numerous reports in the literature of reactions to arsenic, picrate, quinine and quinoline compounds used in the treatment of this infection (3, 6, 18, 23, 28). In one series of 47 cases mentioned in the report of the Council, symptoms had been present for periods ranging from 6 months to 4 years despite various comprehensive methods of treatment (18).

After considering the many reports in the literature on methods of therapy in Trichomonas vaginalis vaginitis, the Council on Pharmacy and Chemistry noted the following common failings: incomplete data on the number of patients, number of complete cures, number of recurrences, number and length of treatments. It especially criticized the lack of control studies and pointed out that while numerous papers report no "failures," there is still no specific therapy. The final conclusion was that the therapeutic objectives at that time should be thoroughness and persistence with the simplest and least messy procedures.

In the 8 years that have followed this comprehensive review, there has been little alteration in the status of pathogenesis, epidemiology or therapy. Trichomonas vaginalis vaginitis has remained an enigma. However, from the mass of confusion certain facts have emerged clearly: (1) Trichomonas vaginalis vaginitis is a definite clinical syndrome; (2) it is quite prevalent with an incidence estimated up to 60 per cent (25); (3) it is capable of producing marked and prolonged discomfort; and (4) an improved method of therapy is needed.

In 1949 we established that aureomycin is trichomonacidal in vitro (21), and similar findings were reported by Greenblatt (12, 13). However, we had observed in many patients that neither Trichomonas intestinalis nor Trichomonas vaginalis were destroyed in vivo when oral aureomycin was administered in therapeutic amounts (22). Therefore, we decided to investigate the effect of the local application of aureomycin into the lower female genital tract. In a previous communication (21), we described encouraging results in 54 instances. This paper constitutes a report of the clinical findings in 95 patients observed at frequent intervals for as long as 20 months after treatment for Trichomonas vaginalis vaginitis with aureomycin. It is believed that additional information has been gathered concerning the pathogenesis and epidemiology of this infection. Efforts have been made to meet the criticisms frequently leveled at therapeutic studies in Trichomonas vaginalis vaginitis.

METHODS

To establish the effectiveness of the local application of aureomycin, 6 nonpregnant patients having symptomatic Trichomonas vaginalis vaginitis were employed as controls. In each case, the vagina was insufflated with 2 grams of powdered talc on 2 consecutive days and insufflation repeated on the fourth and sixth days. Talc was employed because it is an inert substance. At the end of this period, the vaginal secretions were negative for Trichomonas vaginalis in all instances. However, within 8 days all had again become positive. These 6 patients were retreated exactly as before except that each insufflation consisted of 500 milligrams of aureomycin in 2 grams of powdered talc. These patients were examined every 2 weeks for 3 months after treatment and all remained asymptomatic and free of

parasites. Therefore, it was decided to expand this investigation.

Through the co-operation of the Divisions of Medicine, Obstetrics and Gynecology of the University of Tennessee College of Medicine, and the John Gaston Hospital, 63 nonpregnant and 32 pregnant patients were obtained for study. While additional cases were treated, only those patients were included in this series who received the full course of therapy and were observed for a period of at least 3 months after treatment. The diagnosis in every instance was established microscopically in a wet-mount preparation. For this procedure, 1 to 2 drops of vaginal secretion were placed on a clean glass slide, overlaid with a cover slip and examined within 10 minutes. Low magnification was utilized to locate trichomonads by their characteristic motility, and definite identification was established under high magnification. In our hands, cultural methods demonstrated no advantage and so were not employed.

All patients in this series were divided into 2 categories—nonpregnant and pregnant; and a uniform therapeutic regimen was adopted for each group. All nonpregnant patients were insufflated on the first, second, fourth, and sixth days. Thereafter, the patient was instructed to insert a 250 milligram gelatin capsule of aureomycin deep into the vagina every other night for 2 weeks. Pregnant patients were insufflated on the first, second, third, fourth, sixth, and eighth days; thereafter, the patient was instructed to insert a 250 milligram gelatin capsule of aureomycin deep within the vagina every night for 2 weeks. As described previously, the powder for insufflation consisted of 500 milligrams of aureomycin hydrochloride in 2 grams of powdered talc. A Holmes insufflator equipped with a rubber cuff and detachable end piece was employed. Great caution was utilized, especially in pregnant patients, to prevent possible air embolism. The insufflation material was sprayed evenly over the cervix, vagina, introitus, and vulva. Following each treatment, patients were instructed to wear a vulvar pad until the ensuing insufflation and thereafter as was needed to protect clothing. Each patient was instructed to avoid sexual intercourse until therapy was completed. Patients were also advised to refrain from douching during the period of insufflation if possible; and to limit douches to twice a week during the use of intravaginal capsules. For a douche, 60 cubic centimeters of acetic acid (white vinegar) were added to 2 liters of warm water. Efforts were made to examine sexual contacts, but little success was achieved because of the large number of contacts in most of these cases. However, it is of interest that the husbands of 2 patients whose infection had recurred twice were found to harbor Trichomonas vaginalis. After these men had been successfully treated with oral aureomycin, both women responded excellently to the local use of this antibiotic.

Following treatment every patient was requested to return to the clinic in 2 weeks and thereafter each month. Naturally, many did not adhere to this schedule. It is quite difficult to obtain the prolonged co-operation of a large group of women who no longer have symptoms of disease. By and large, however, co-operation was very good. When a patient failed to return within 2 months, efforts were made to contact her by telephone, by mail or, if necessary, through a social worker.

We believe that in such an infectious condition as Trichomonas vaginalis vaginitis, it is useless to follow treated cases for more than 1 year. This would appear to be especially true when, as in this series, the patients are from the lowest economic and social strata. After 1 month, it is quite difficult to distinguish between relapse and reinfection. However, we believed that much could be learned about the epidemiology of this infection by prolonged observation; furthermore, it was interesting to observe pregnant patients before and after delivery. We adopted as our arbitrary criteria for cure freedom from symptoms and parasites for at least 3 months. During this period, a minimum of 4 negative examinations were required.

THERAPEUTIC RESULTS IN NONPREGNANT PATIENTS

Sixty-three nonpregnant patients having Trichomonas vaginalis vaginitis were treated by the local application of aureomycin as

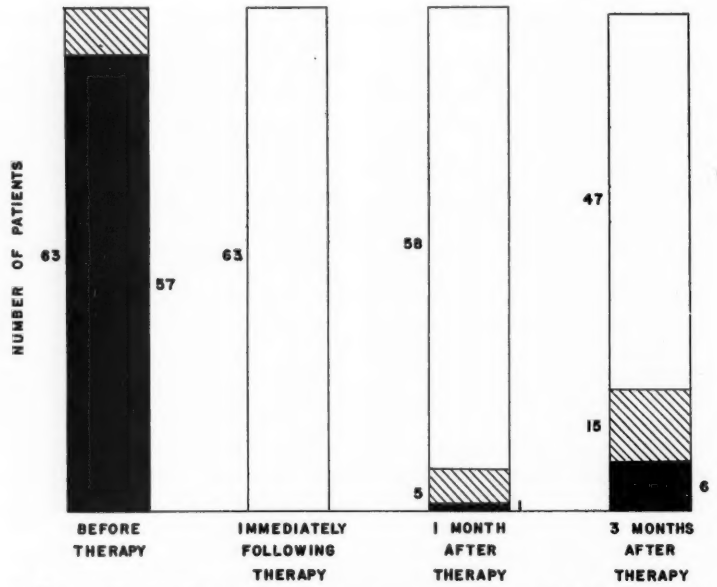

Fig. 1. Therapeutic response of nonpregnant patients treated with intravaginal aureomycin. Cross hatched areas, patients infected with Trichomonas vaginalis vaginitis; black areas, infected patients manifesting symptoms of Trichomonas vaginalis vaginitis; white areas, noninfected and asymptomatic cases.

described. Sixty were negroes and 3 were white. Of these, 49 were symptomatic. The most frequent complaints were leucorrhea, pruritus, polyuria and dyspareunia. Examination of the 14 "asymptomatic" patients disclosed a rather profuse vaginal discharge in 8 instances with definite evidence of an associated inflammatory reaction in 6 of these. Only 6 cases, therefore, could actually be regarded as asymptomatic. The character of the vaginal discharge in this group varied from thin and watery to thick and yellow; in essentially all, a foul odor was noted. The frequently described foamy discharge was observed in only 28 patients. With 1 exception, all of these cases were followed for at least 3 months after treatment and were examined a minimum of 4 times. One patient died of a coronary occlusion 2 months following therapy, but she had been examined on 4 occasions. Forty cases in this category were observed for over 6 months, 36 for over 9 months, 33 for over 12 months, 21 for over 15 months, and 10 for over 18 months. The longest observation period was 20 months and involved 21 examinations.

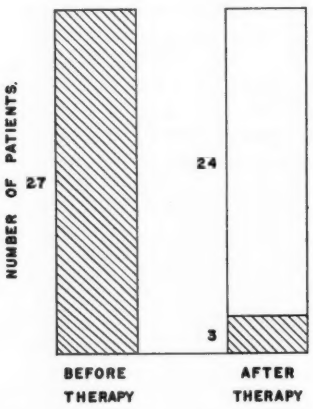

Fig. 2. Therapeutic response of retreated nonpregnant patients. Only 3 cases failed to meet our arbitrary criteria for cure.

Immediately after treatment and for the ensuing 2 weeks, all 63 patients were free of

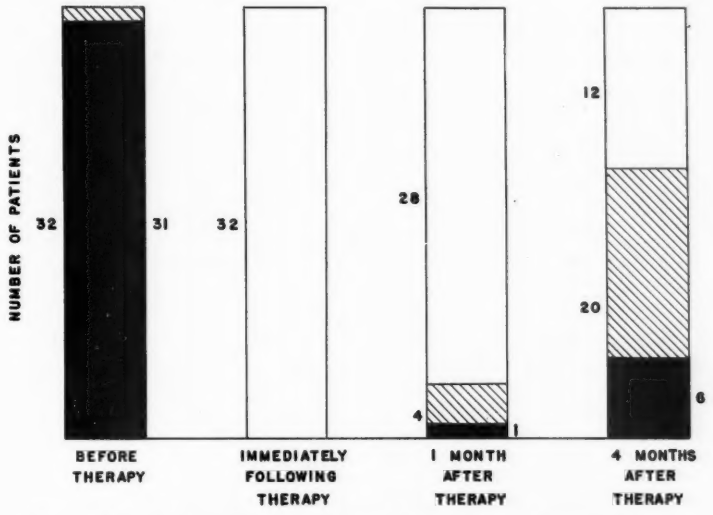

Fig. 3. Therapeutic response of pregnant patients treated with intravaginal aureomycin. Cross hatched areas, patients infected with Trichomonas vaginalis; black areas, infected patients manifesting symptoms of Trichomonas vaginalis vaginitis; white areas, noninfected and asymptomatic cases. The 4 month table represents an average.

trichomonads and were asymptomatic. At 1 month, 5 were found to harbor Trichomonas vaginalis but only 1 was symptomatic. By the end of 3 months, 10 additional cases were positive with definite symptoms being observed in half of them. During a period of 18 months, 27 patients were found to be infected with Trichomonas vaginalis; but of this number 15 were asymptomatic. There was, therefore, a marked reduction in symptoms in those who did become positive after treatment (Fig. 1).

All patients who were found to harbor Trichomonas vaginalis were immediately retreated exactly as before. While it was necessary to retreat 7 patients twice and 2 others 3 times, only 3 patients failed to remain asymptomatic and free of trichomonads for at least 3 months (Fig. 2).

THERAPEUTIC RESULTS IN PREGNANT PATIENTS

Thirty-two pregnant patients having Trichomonas vaginalis vaginitis were treated with intravaginal aureomycin as described previously; 28 were negroes and 4 were white. Four patients, in this category, became pregnant while under observation following therapy for trichomoniasis; all 4 became positive, symptomatic, and required retreatment. We were able to observe 25 patients for varying periods before and after delivery. Only 1 patient in this group was regarded as asymptomatic prior to treatment. The chief complaints of these women were profuse, foul-smelling leucorrhea and associated pruritus.

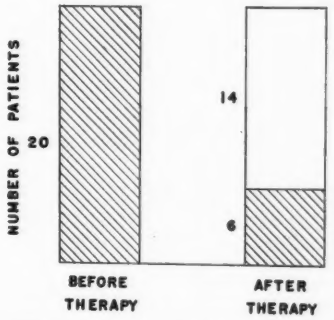

Fig. 4. Therapeutic response of retreated pregnant patients. Six patients failed to meet our arbitrary criteria for cure.

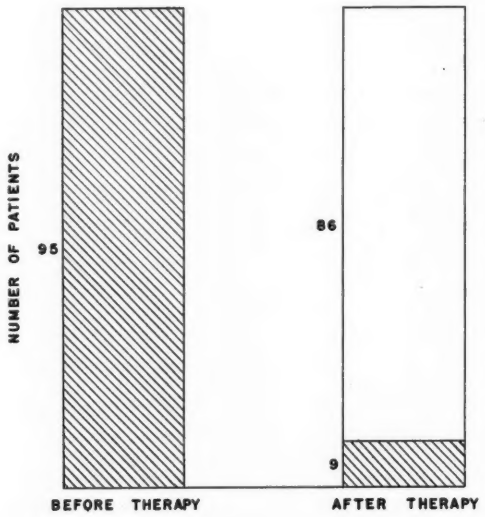

Fig. 5. Summation of therapeutic results. Cross hatched areas represent patients infected with Trichomonas vaginalis. Of 95 patients treated with intravaginal aureomycin only 9 failed to meet our arbitrary criteria for cure.

In more than half of these patients, the symptoms were quite severe.

Following complete treatment, all became free of trichomonads for 2 weeks but, thereafter, the relapse or reinfection rate was much higher than in the nonpregnant group. The observation period in this category ranged from 1 to 7 months antepartum; and in 25 cases the postpartum follow-up ranged from 1 to 10 months. One month after treatment 4 patients were found to harbor Trichomonas vaginalis; by 2 months, 8 additional patients were infected. Twelve patients remained free of trichomonads throughout their pregnancy (Fig. 3). While it was necessary to retreat 20 cases, the relief of symptoms in all was quite satisfactory. Retreatment was required twice in 3 instances and 3 times in 1 case. Nevertheless, when the same criteria for cure in this category as in the nonpregnant group were used, successful results were obtained in 26 of the 32 patients (Fig. 4).

In no instance was there any indication of a deleterious effect on pregnancy. While a greater number of insufflations was required in this group, extreme caution was observed.

DISCUSSION

Despite the paucity of knowledge concerning the pathogenesis and epidemiology, it is definitely established that Trichomonas vaginalis vaginitis constitutes a prevalent and troublesome clinical entity. Inasmuch as there is an obvious need for an improved method of treatment, we decided to investigate this problem. After it was established that aureomycin is trichomonacidal in vitro, its clinical effectiveness was studied.

Sixty-three nonpregnant and 32 pregnant patients were treated by the local application of aureomycin into the lower female genital tract. Eighty-eight of these were negroes and 7 were white. While only 70 of these patients volunteered symptoms referable to Trichomonas vaginalis vaginitis, examination revealed definite evidence of an inflammatory reaction in 88. It is our opinion that the mental attitude of the patient is an extremely important factor in the evaluation of symptomatology.

A definite therapeutic regimen was followed and control studies were carried out. Efforts were made to eliminate frequent failings in therapeutic studies in Trichomonas vaginalis vaginitis.

The posttherapeutic observation period in the nonpregnant group ranged from 3 to 20 months. In the pregnant category, it ranged from 1 to 7 months antepartum and, in 25 cases, from 1 to 10 months postpartum. Only 3 nonpregnant and 6 pregnant patients failed to meet our arbitrary criteria for cure—absence of symptoms and parasites for at least 3 months (Fig. 5). Even in these 9 cases, however, there was definite amelioration of symptoms. When the highly infectious nature of Trichomonas vaginalis vaginitis and the poor economic and social status of our patients are considered, these results are quite good. It is very difficult to distinguish between relapse and reinfection in this condition; after 1 to 2 months it is practically impossible. Though efforts were made to examine sexual contacts, little success was achieved. However, in 2 refractory cases the husbands were found to be infected and no recurrence followed treatment of both the men and their wives. The importance of personal hygiene was repeatedly stressed to our patients. While the recurrence

rate was much higher in the pregnant group, the relief of symptoms was most gratifying. Caution in vaginal insufflation during pregnancy must be emphasized.

No significant toxic reactions to intravaginal aureomycin was observed. In 16 of 95 cases, mild discomfort as pruritus, burning or mild intravaginal pain was noted after therapy; but these symptoms could not always be definitely attributed to the medication. There was no demonstrable adverse effect on pregnancy. In 5 instances, aureomycin blood levels were obtained 3 hours after intravaginal insufflation with 500 milligrams of aureomycin in powdered talc. In 3 cases there was no evidence of this antibiotic, while in 2 it was only 0.12 microgram per cubic centimeter of blood.

Despite progress in therapy, much additional fundamental information is needed concerning the natural history of this infectious disease. At present, a large group of isolated patients having Trichomonas vaginalis vaginitis is being comprehensively studied with regard to vaginal bacteriology, vaginal acidity, cell morphology, sexual contacts, and personal hygiene. In this series, a suppository is being employed rather than the gelatin capsule used in the investigations reported in the present paper. This therapeutic modification results in a wider and more uniform distribution of the medicinal agent thereby preventing the possibility of irritation due to concentration of the antibiotic in a small area. After repeated attempts, a nonirritable suppository for home use has been prepared for us composed of white wax, paraffin, lanolin, and petrolatum. Each suppository contains 250 milligrams of aureomycin; a similar amount of mixed parabens is added as an inhibitor of Candida albicans (Monilia albicans). Preliminary bacteriologic studies following the intravaginal use of aureomycin powder and suppositories indicate that this method of treatment should also be of value in pyogenic infections involving the lower female genital tract.

There is no more frequent and troublesome problem in general medicine, obstetrics and gynecology than Trichomonas vaginalis vaginitis. Because of the ease and simplicity of administration, rapidity of clinical response and lack of toxic effects, the local application of aureomycin appears to afford an excellent mode of treatment for this common infection.

SUMMARY

1. Ninety-five patients having Trichomonas vaginalis vaginitis were treated by the local application of aureomycin into the lower female genital tract. Sixty-three of these patients were nonpregnant and 32 were pregnant; 88 were negroes and 7 were white.

2. Eighty-six cases of Trichomonas vaginalis vaginitis treated with intravaginal aureomycin met our criteria for cure.

3. No significant toxic reactions to aureomycin were observed.

4. Aureomycin appears to be an effective therapeutic agent in Trichomonas vaginalis vaginitis.

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CUTANEOUS HISTAMINE REACTION AS A TEST OF CIRCULATORY EFFICIENCY OF TUBED PEDICLES AND FLAPS

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IN a report by Conway, Stark, and Docktor (1949) attention was called to the parallelism between the state of the collateral circulation in an extremity with peripheral vascular disease and that of the developing circulation of tubed pedicles or flaps of soft tissue. In the management of peripheral vascular disease, the relative efficiency of the circulation has been measured by the use of a variety of tests including the saline wheal test, the temperature-return test, the vaso-occlusion index and others. Conway, Stark, and Docktor reported observations on the saline wheal test, the fluorescein test and a modification of the temperature return test in the evaluation of the circulatory efficiency of tubed pedicles. The conclusion was reached that the saline wheal test and the fluorescein test give more accurate evaluation of the efficiency of circulation of a tubed pedicle or flap than do clinical observations alone. The problem in the surgery of transplantation of soft tissue is to determine the earliest date (after construction of a flap or pedicle) at which it may be transplanted successfully. The number of days required for a given pedicle or flap to achieve physiologic maturity varies not only with its type, the ratio of its length to width, the size and the anatomical location of the structure but also with the physical status of the patient, as affected by age, state of nutrition, and peripheral circulation.

Work on this problem has been presented by Douglas who applied a test which measured the return to normal of the temperature of the subcutaneous tissue following release of a tourniquet applied previously to both ends of a tubed pedicle. Douglas and Bucholz measured the rate of return to normal femoral levels of the systolic blood pressure in a tubed pedicle previously occluded by tourniquet. Douglas and Millikan used a photo-electric oximeter upon tubed pedicles to appraise the development of circulation by measure of the rate of flow of blood into a pedicle following release of a tourniquet. Utilizing a method described by Lange for measuring circulation time and for appraising the vascularity of granulating wounds, Dingwall and Lord used intravenous sodium fluorescein to demonstrate the degree of vascularization of tubed pedicles. Hynes injected 1/25 grain of atropine into pedicles and recorded the time required for the appearance of the symptoms and signs of the systemic effect of the drug. Hynes and MacGregor reported on the use of the fluorescein method of Dingwall and Lord and, in addition, reported their experiences with fluorescein visualization of histamine dermal wheals as described earlier by Neller and Schmidt. Olander described a nicotinic acid and epinephrine test to determine the direction of flow of blood in flaps, and to determine the presence of collateral circulation across barriers of scar tissue formed in healed incisions.

Objections to the saline wheal test are that it requires approximately 1 hour for execution and that its end point, the complete resorption of the wheal, is determined with difficulty. The fluorescein test is difficult to perform in many hospitals because the use of a dark room and ultraviolet light are required. In addition, the patient may complain of nausea or of the yellow coloration produced by the intravenous injection of fluorescein.

This presentation is made in order to set down observations on the use of the cutaneous histamine reaction as a measure of circulatory

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TABLE I.—RESULTS OF TESTS IN 18 PATIENTS

Case No.	Age of patient years	Defect	Type of pedicle	Anatomical location of pedicle	Ratio length width	Days after construction	Result of cutaneous histamine test	Result of surgical transplantation	Remarks
1	35	Compound fracture, tibia, with nonunion and unstable scar	Open flap	Medial calf (cross leg)	1:1	20	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
2	28	Deep preauricular and aural defect	Tubed pedicle	Cervical	3:1	28	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
3	52	Loss of mandible, chin and larynx	Tubed pedicle	Trunk (thoracoepigastric)	3:1	35	Wheal developed in pedicle as soon as in control area	Successful 2 days following test	Patient severely emaciated
4	19	Binding scar of wrist	Open pedicle	Abdomen (direct flap)	1:1	15	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
5	56	Through-and-through defect of cheek	Open pedicle	Pectoral (thoracoacromial)	1.5:1	49	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	Positive Wassermann. Patient discharged from hosp., 1 month between operative stages; developed cerebrovascular accident
6	52	Loss of symphysis mentis and chin	Tubed pedicle	Pectoral (thoracoacromial)	1:1	37	Wheal developed in pedicle as soon as in control area	Successful 9 days following test (1st transplantation)	Patient discharged from hospital 1 week because of illness in family
						66	Wheal developed in pedicle as soon as in control area	(2nd transplantation)	
7	66	Loss of orbit, maxilla and ethmoid sinus, right	Open pedicle	Temporal (delayed)	2:1	21	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
8	24	Compound fracture tibia, with nonunion and unstable scar	Open flap	Anterior thigh (cross thigh flap)	1.5:1	18	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
9	24	Unstable scar over tibial crest	Open flap	Medial calf (cross leg)	1:2	24	Wheal developed in pedicle as soon as in control area	Successful 6 days following test	
10	20	Unstable scar over tibial crest	Cross leg flap	Medial calf (cross leg)	1:1	19	Wheal developed in pedicle as soon as in control area	Successful 5 days following test	
11	68	Partial defect of nose, maxilla, and lower lip	Tubed pedicle	Pectoral (thoracoacromial)	1.5:1	52	Wheal developed in pedicle as soon as in control area	Successful 2 days following test	Patient had moderate arteriosclerosis
12	54	Partial defect of nose, eye, and cheek	Open flap	Temporal (delayed flap)	2:1	48	Wheal developed in pedicle more slowly than in control area	Flap elevated and returned to original bed 1 day later because of cyanosis of pedicle (1st operation)	Discharged from hospital for 2 months between operative stages; patient had moderate arteriosclerosis and marked obesity
						130	Wheal developed in pedicle as soon as in control area	Successful 1 day following test (2nd operation)	
13	64	Pharyngostome	Tubed pedicle	Pectoral (thoracoacromial)	1.5:1	100	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	Transplantation delayed because of homologous serum jaundice
14	57	Loss of soft tissue of entire nose	Tubed pedicle	Pectoral (thoracoacromial)	2:1	4	Wheal developed in pedicle more slowly than in control area	Pedicle divided 1 day following test and resutured to its bed. Transplanted successfully 11 days later	Severance of tubed pedicle successfully accomplished at 11 days as prognosticated by test, but cyanosis of pedicle indicated that it would not withstand the additional strain of transplantation
						11	Wheal developed in pedicle as soon as in control area		

TABLE I.—RESULTS OF TESTS IN 18 PATIENTS—Continued

Case No.	Age of patient	Defect	Type of pedicle	Anatomical location of pedicle	Ratio length width	Days after construction	Result of cutaneous histamine test	Result of surgical transplantation	Remarks
15	50	Oral cutaneous fistula of cheek	Tubed pedicle	Pectoral (thoracoacromial)	2:1	20	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	Chronic alcoholic
16	46	Oral cutaneous fistula of cheek	Tubed pedicle	Pectoral (thoracoacromial)	2:1	23	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	Positive Wassermann test; chronic alcoholism and arteriosclerosis
						44	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
17	65	Loss of soft tissue of one half of nose and upper lip	Open flap	Temporal (direct flap)	3:1	20	Wheal developed in pedicle as soon as in control area	Successful 1 day following test	
18	59	Right ala and lower half of right upper lateral cartilage	Oblique forehead pedicle	Right side forehead	2:1	13	No wheal formed	Successful 1 day following test	
						14	No wheal formed		
						16	Wheal developed in pedicle more slowly than in control area		
						17	Wheal developed in pedicle as soon as in control area		

efficiency in tubed pedicles and flaps and to point out the advantages of this test over those listed herein.

The development of the cutaneous histamine reaction as a test for collateral circulation resulted from the work of Sir Thomas Lewis who showed that stroking the skin initiated a triple response. The onset is the "white reaction" which consists of the blanching of the skin due to the constriction of minute venules. The "red reaction" which follows is said to be due to dilatation of venules, capillaries, and terminal arterioles. A stronger "red reaction," termed a "flare reaction," is quantitatively different from the former in that the larger arterioles are dilated. This is believed to be due to action of a histamine-like substance upon the sympathetic nerve endings, and it is dependent upon an intact nerve supply. This histamine-like substance also causes a change in the walls of the vessels producing a local wheal by transudation of plasma. A wheal does not form unless an adequate flow of blood is present and its formation is independent of innervation. The interval of time required for the triple response is an index to the status of the peripheral circulation. A rapid appearance of these phenomena denotes well developed circulatory efficiency. Maximal response is effected in normal tissue in from 5 to 8 minutes. The cutaneous histamine reaction was used by Starr and by deTakats to test the circulation in peripheral vascular disease.

METHOD

After scarification of a small area of cutaneous surface by needle, a drop of the acid phosphate salt of histamine (1:1000) is applied. This is done at a number of places over the tissue under consideration. The number of minutes required for the development of the cutaneous wheal in the tissue under observation has been compared with a control area as an index of its circulatory efficiency. We have adapted this test for tubed pedicles and flaps, performing histamine scarification at the end of the pedicle to be transplanted after its occlusion by tourniquet. A control test is done in the skin of the same anatomical region on the opposite side of the body. The surgical construction of a pedicle or flap may result in its denervation so that the "flare reaction" often is absent. If the control is placed upon the "flush area" of the head or neck, often the wheal appears in less than 8 minutes. By experience we have found that if a wheal forms in less than 8 minutes, at the distal end of the

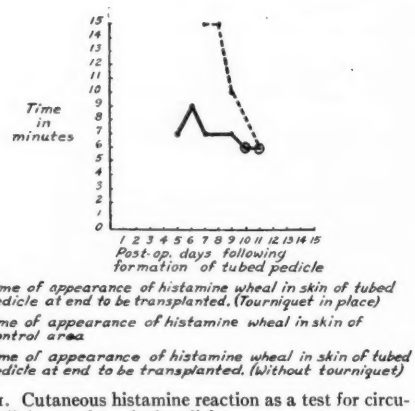
Time in minutes
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Post-op. days following formation of tubed pedicle
---- Time of appearance of histamine wheal in skin of tubed pedicle at end to be transplanted. (Tourniquet in place)
—— Time of appearance of histamine wheal in skin of control area
o Time of appearance of histamine wheal in skin of tubed pedicle at end to be transplanted. (Without tourniquet)

Fig. 1. Cutaneous histamine reaction as a test for circulatory efficiency of a tubed pedicle.

pedicle to be transplanted, the pedicle will withstand transplantation successfully. This observation liberalizes the criterion for successful transplantation. Wheals do not form readily on the thick skin of the forehead. Therefore the test must be read carefully in that region. If the rate of appearance of the wheal at the obstructed end of the pedicle approximates that of the control, the pedicle should undergo surgical transplantation successfully. The time of maximum wheal formation is approximately 8 minutes. We have performed this clinical test 31 times upon 18 patients and in all of these cases the test has been found to be reliable (Table I). This test has the advantages that it can be done quickly, does not damage the pedicle, requires no elaborate apparatus and possesses a positive end-point.

Consideration of Table I shows that in those cases in which the histamine wheal appeared in the skin of the tubed pedicle or flap as quickly as in the control area, the tissue was transplanted successfully. In Case 12 the histamine wheal required more time for its appearance than was required in the control area. Following that test the pedicle showed distinct cyanosis when it was elevated from its bed. Subsequently the test indicated that the tourniqueted tissues of the flap enjoyed circulatory efficiency equal to that of the control area and the flap was transplanted successfully.

Figure 1 gives a graphic presentation of the practical application of the cutaneous histamine reaction as a test of circulatory efficiency in reconstructive surgery of soft tissue.

G. McW. (NYH Case 572822), white, male, age 57, was subjected to operation on July 5, 1950, at which time a tubed pedicle was constructed in the right acromiopectoral region. This pedicle measured 10 centimeters by 5 centimeters. The cutaneous histamine reaction was studied daily from the fifth postoperative day. As shown on the chart (Fig. 1) (Table I, Case 14) there was no wheal formation on the skin of the pedicle near the point of application of the tourniquet on the fifth and sixth postoperative days. On the seventh postoperative day wheal formation appeared in 15 minutes as compared with 7 minutes required for wheal formation in the control areas. On the eleventh postoperative day the wheal appeared on the tourniqueted pedicle as rapidly as on the control area, that is, within 6 minutes. A further refinement of interpretation of the test was developed in that the appearance rate of the wheal on the end of the pedicle to be transplanted was found to be the same (6 minutes), whether or not the circulation of that end of the pedicle was cut off by tourniquet. With this evidence that the pedicle was ready for complete section, the patient was taken to the operating room where the pedicle was divided successfully, 12 days after its construction.

SUMMARY AND CONCLUSIONS

The cutaneous histamine reaction, which has been used as a test of collateral circulation in peripheral vascular disease of the extremities, has been applied to the evaluation of circulation in tubed pedicles and flaps preparatory to their division and surgical transplantation. The test has been used 31 times in 18 patients. Information as to circulatory efficiency as gained from this test has been found to be reliable in all of the 18 cases. The cutaneous histamine reaction is looked upon as a good clinical test for the circulatory efficiency of soft tissue prepared as flap or pedicle for transplantation. In the opinion of the authors it is superior to the saline wheal test and to the fluorescein test.

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ELECTROPHRENIC RESPIRATION

VII. The Motor Point of the Phrenic Nerve in Relation to External Stimulation

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IT has recently been demonstrated that the intermittent electrical stimulation of one phrenic nerve through the intact skin is capable of producing effective and readily controlled artificial respiration (electrophrenic respiration, or EPR). Previous studies in the cat, rat, rabbit, dog, monkey, and man revealed that: (a) Tidal volume is proportional to the peak voltage applied. (b) The respiratory rate and duration of inspiration can be readily varied within satisfactory limits. (c) All spontaneous respiratory activity ceases immediately after the onset of electrophrenic respiration and, if originally present, returns when electrophrenic respiration is discontinued. (d) The lung on the unstimulated side is ventilated almost as much as the lung on the side of the stimulated phrenic nerve by virtue of mediastinal shift. (e) During hemorrhagic shock or high spinal anesthesia in man and dogs, electrophrenic respiration maintains the circulation at a more satisfactory level than positive pressure breathing, presumably because it is similar to normal respiration and causes breathing by decreasing intrapleural pressure. (f) The reserve of the method is such that it is generally possible to triple the normal resting respiratory minute volume, with the submaximal stimulation of one phrenic nerve in the absence of spontaneous respiration. (g) Preliminary studies revealed that, because of the ability of electrophrenic respiration to suppress the respiratory center reflexly, it can completely inhibit the troublesome respiratory irregularities of patients with bulbar poliomyelitis and either maintain adequate ventilation by itself or help adapt the patient to the tank respirator. (h) The nursing care of apneic patients has been found easier if the patient is breathed by means of electrophrenic respiration than if enclosed in a tank-type respirator. (i) It is an effective experimental method for producing pulmonary ventilation without the use of positive pressure (1, 2, 4–11).

The main drawbacks of this method to date have been the following: (a) Patients with both phrenic nerves incapacitated by disease cannot be breathed by electrophrenic respiration. (b) The electrical toxicity to nerve during prolonged periods of stimulation has not yet been thoroughly studied although work in other laboratories is encouraging in this regard. (c) The emergency application of electrophrenic respiration is of only limited usefulness in the hands of those who have not become proficient in locating the motor point of the phrenic nerve.

The purpose of this report is to describe the technique by which electrophrenic respiration can be rapidly and effectively applied, and to present data on the time required for initiating artificial respiration.

METHOD

Anatomical and technical considerations. 1. Motor point of the phrenic nerve. The phrenic nerve passes medially over the lateral edge of the anterior scalene muscle before it assumes its downward course on the anterior surface of the anterior scalene muscle. It is at this point, where the nerve passes around the lateral edge of the scalene onto its anterior surface, that stimulation can be most readily achieved (the motor point). In a small percentage of cases, the phrenic nerve, after

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reaching the anterior surface of the anterior scalene muscle, courses further medially, so that it is almost on the medial aspect of that muscle. Occasionally, therefore, it may be necessary to press the exploring index finger firmly toward the medial portion of the scalene ridge to establish optimal contact.

The motor point of the phrenic nerve lies *beneath* the sternocleidomastoid muscle, and the success of the operator in promptly starting respiration depends to a large extent on his awareness of the necessity for avoiding interposition of the sternocleidomastoid by displacing it medially when he attempts to contact the motor point, so that the current does not have to pass through anything but skin and platysma. *By far the most frequent source of error is caused by overlooking the lateral or clavicular insertion of the sternocleidomastoid muscle since this is often in the form of a flat band which may be unnoticed unless specifically looked for.*

2. The optimal position of the operator. The operator should be seated in the conventional anesthetist's position at the head of the bed or table on which the patient lies (Fig. 1). The respirator should be placed on the side opposite to the nerve being stimulated, so that it is convenient for the operator to manipulate the controls by touch without having his attention distracted from the patient's diaphragm. The indifferent electrode is *thoroughly* wetted and either slipped under the shoulder of the patient or fixed in place with Scotch or adhesive tape (Fig. 2). The stimulating thimble electrode (Fig. 4) is wetted with saline.

3. Position of the patient's head. It is advisable to position the head so that the *sternocleidomastoid muscle is completely relaxed and therefore readily moved medially.* The head should be (a) in the midline, looking straight ahead, and (b) slightly elevated from the table by a pillow or any suitable object so that the head *and* neck are slightly flexed (Figs. 3a and 3b). Simply elevating the head end of the bed as by "gatching up" does not produce this desired relaxation.

4. Position of the stimulating electrode on the finger. The thimble electrode should be drawn snugly on the index finger so that the electrode itself is over the tip of the finger and effectively becomes a part of the finger which is feeling for the scalene ridge (Fig. 4). When the motor point has been found and respiration started, the pressure of the stimulating finger can be lightened. The operator's hand is placed on the pillow adjacent to the patient's neck in a relaxed position so as to permit prolonged stimulation.

5. Exploration for the motor point. This should begin about one-third of the way between clavicle and mastoid, *not* just above the clavicle where one is tempted to start. The point at which the phrenic nerve crosses the lateral ridge of the anterior scalene varies somewhat, and therefore the ridge should be explored upward and downward. The point just below where the external jugular vein crosses the lateral margin of the clavicular portion of the sternocleidomastoid muscle is most likely to yield a prompt response and should be used as the initial site of exploration, it being necessary to remember that the electrode on the tip of the exploring finger should be advanced onto the scalene ridge behind the sternomastoid muscle.

If cervical or brachial plexus motor activity occurs initially, this may be used as a helpful sign because it informs the operator that his exploring finger is too far laterally. Under these circumstances the finger should be moved medially on the anterior surface of the anterior scalene muscle, since at that point the phrenic is isolated and therefore relatively insulated from all other nerves in that locality. In an emergency, the occurrence of motor activity of other nerves along with that of the phrenic nerve is of little consequence. After respiration has been initiated, attempts to place the stimulating electrode solely on the phrenic motor point are then appropriate.

In practicing on a normal subject it is well to ask him to raise his head off the table, thus calling the sternocleidomastoid muscle into play. The lateral margin of the clavicular portion of that muscle can then be readily identified and displaced medially by the exploring finger. Fortunately, the scalene ridge is backed by the transverse processes of the vertebrae and thus forms an easily palpated bony landmark. After some practice, the head-raising maneuver becomes unnecessary.

TABLE I.—"EXPLORE" TIMES ON 24 CONSECUTIVE VOLUNTEER SUBJECTS FOR EPR

Number	Subjects	Sex	Explore time seconds	Age years	Height ft.	Height in.	Weight pounds
1	C. A.	F	3.0	28	4	10½	104
2	B. C.	F	4.0	26	5	6	132
3	J. C.	M	3.0	20	5	10½	175
4	E. D.	F	10.0	27	5	4	115
5	H. H.	M	4.0	47	5	8	180
6	N. J.	F	8.5	31	5	6	145
7	B. K.	F	2.0	26	5	3	105
8	N. M.	M	45.0	24	6	1	160
9	J. M.	M	4.5	23	5	10	190
10	M. M.	F	4.0	35	5	2½	122
11	M. M.	M	6.0	37	5	10	180
12	G. N.	M	14.0	36	5	8	270
13	M. S.	F	5.0	38	5	6½	155
14	E. V.	F	4.0	21	4	10½	104
15	C. V.	M	2.0	26	5	9	160
16	M. W.	M	3.0	24	6		165
17	C. W.	M	5.0	24	5	8	155
18	E. K.	M	3.5	39	5	7½	185
19	M. R.	M	6.0	43	5	9½	183
20	R. T.	M	7.0	33	5	7	170
21	T. S.	M	21.0	48	5	7	160
22	H. G.	M	6.0	31	6		195
23	J. C.	M	3.5	26	5	1	145
24	A. R.	M	3.0	38	6		190

Average 7.4

If, during the course of exploring for the motor point, there should be a contraction of any of the neck muscles, it will be apparent that the electrode is over the motor point of one or more of these muscles. The electrode position should then be altered slightly and the approach to the scalene ridge made from a slightly different direction.

The same considerations apply to cutaneous sensation. Usually, during electrophrenic respiration, the only sensation is a mild local tingle which tends to diminish after a few minutes. Occasionally, however, the electrode may be placed directly on one of the cutaneous cervical nerve trunks, in which case the electrode position on the skin should be slightly altered in order to avoid the attendant discomfort. It is apparent that this factor is of little or no importance in the treatment of the patient with acute respiratory paralysis.

The omohyoid muscle being a double bellied muscle which narrows to a slender tendon in the area of the phrenic motor point is of no consequence.

6. The index finger wearing the electrode should be facing posteriorly, not medially, when the exploration for the motor point takes place (Fig. 5). This permits better contact with the anterior surface of the anterior scalene muscle. The medial aspect of the exploring index finger is used to displace the sternocleidomastoid muscle medially and hold it out of the way while the tip of this finger holds the thimble electrode in contact with the phrenic nerve.

7. Use of the pen electrode and bedside clamp for prolonged stimulation. If one is called upon to treat patients with electrophrenic respiration and to maintain contact with the motor point of the phrenic nerve over a period of several hours, it is desirable to be able to change the position of one's hand, and this may be accomplished by using a pen-type electrode (Fig. 6a). Further, by attaching a gooseneck clamp to the bed or table and fixing the pen electrode at its end, it is possible to maintain effective motor point contact in the quiet patient without manually holding the electrode in place (Fig. 6b). A significant percentage of patients in respiratory failure (cerebrovascular accidents, brain tumor, barbiturate poisoning) are sufficiently quiescent to make this an effective method. It requires, however, the frequent presence of an observer or nurse trained in this method, since a slight motion may displace the electrode and thereby alter or abolish the respiratory response, thus requiring repositioning of the electrode.

8. Time required for localization of the phrenic motor point in 24 consecutive volunteers. Encouraged by the improvements in ease of rapidly initiating respiration which had met our efforts, we decided to determine precisely how long it takes to find the phrenic motor point. The experiments were carried out as follows. The "patient" was placed in the supine position on a bed, with the operator (S.J.S.) seated at the head of the bed. The

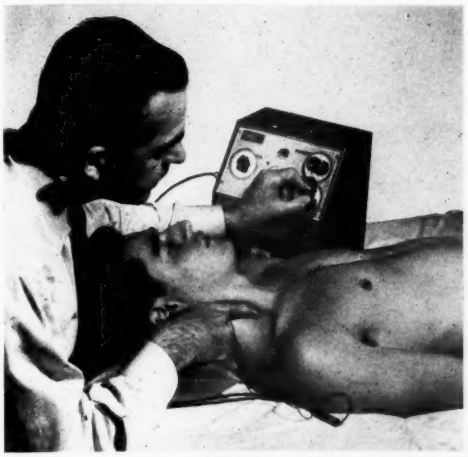


Fig. 1.

Fig. 2.

Fig. 3a.

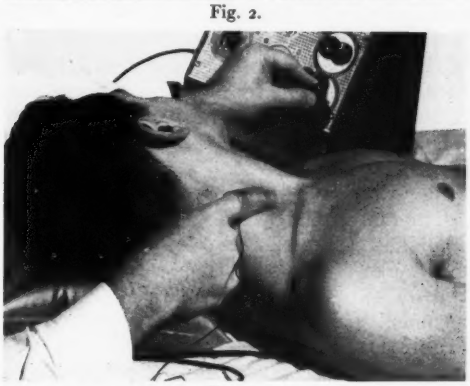


Fig. 3b.

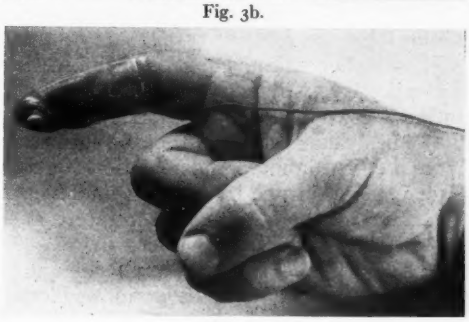


Fig. 4.

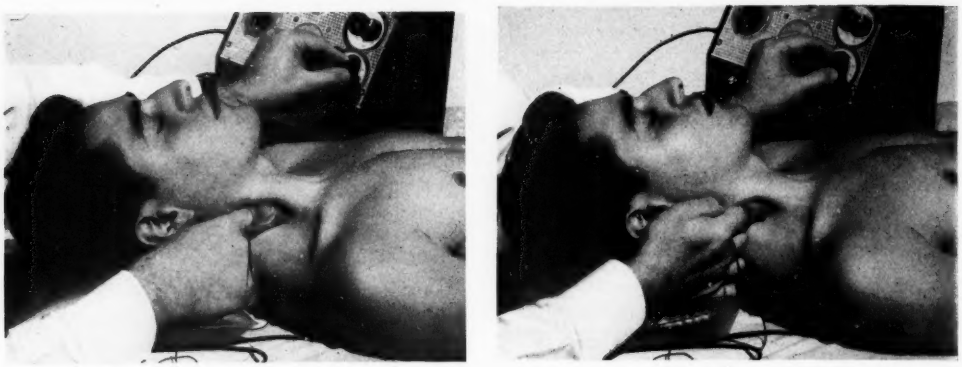
Fig. 1. Correct position of operator, patient, and respirator while exploring for phrenic motor point. The operator manipulates the controls by touch while continuously observing the abdominal area for the first sign of induced diaphragmatic activity and phrenic motor point contact.

Fig. 2. The wetted indifferent electrode secured in place behind the shoulder. In an emergency or in leisurely practice the weight of the patient can be relied upon to maintain contact if the electrode is placed well down behind the shoulder.

Fig. 3. a, Correct head position has as its objective the relaxation of sternocleidomastoid muscle. Head faces forward and is elevated slightly. b, Incorrect head position: puts sternocleidomastoid on the stretch.

Fig. 4. Thimble electrode. The cloth covered metal tip is insulated from finger. The tip should be wetted to conduct properly.

respirator was placed as pictured in Figure 1, and the operator wore the wetted thimble electrode with the power switch on the "explore" setting. An attempt was made to ascertain the "explore" time necessary for locating the phrenic motor point. The stopwatch was started just as the operator moved the thimble electrode toward the neck of the



a b

Fig. 5. a, Correct position of exploring index finger. Tip of finger and electrode face posteriorly so as to contact anterior surface of anterior scalene. b, Incorrect position of tip of exploring finger: it faces medially instead of posteriorly.

subject. It was stopped when the first definite diaphragmatic contraction was observed. Immediately thereafter the power switch was turned to the "breathe" setting and effective pulmonary ventilation initiated. The time was recorded as the "explore" time.

RESULTS

The motor point was found in all instances. The shortest "explore" time was 2 seconds. The longest "explore" time was 45 seconds, and on second try in this subject it was 10 seconds. The average time was 7.4 seconds (Table I). In 87 per cent, respiration was started in 10 seconds or less.

DISCUSSION

These data confirmed our recent impression that effective pulmonary ventilation can be initiated consistently in a short time if the anatomical details of the position of the phrenic nerve are kept in mind and attention given to placing the electrode behind and underneath the lateral margin of the *clavicular* insertion of the sternocleidomastoid muscle.

It is almost axiomatic that any technique of artificial respiration will be performed more effectively in an emergency situation if the operator has had previous practice with the method. This is especially true of electrophrenic respiration. It is the authors' firm opinion that unless the physiological advantages (1, 2, 4, 7–9) of electrophrenic respiration are considered sufficiently compelling to merit the investment of time for practice, the operator would be best advised to use some other method in an emergency.

Bradycardia has not been observed during electrophrenic respiration, and, since this would inevitably accompany vagal stimulation if it occurred, it seems reasonable to conclude that vagal stimulation has not been produced.

For those situations such as in ambulances, transferring apneic patients to the operating room, areas where direct current is likely to be a problem, and for general field use, a battery or field model electrophrenic respirator can be used.

After proficiency has been achieved in starting artificial respiration with the patient on his back, practice will make it possible to start electrophrenic respiration with the patient in the conventional Schaefer prone pressure position. Drawing the patient's knees up slightly, so as to permit observation of the diaphragm, is helpful. It is to be imagined that this would be the position of preference for patients in whom drainage of the pharynx is desirable, as, for example, after drowning.

For long term stimulation (days), the implantation of a polyethylene covered tantalum electrode in the vicinity of the phrenic nerve has been shown to be an effective method. This method will be described in a future communication.

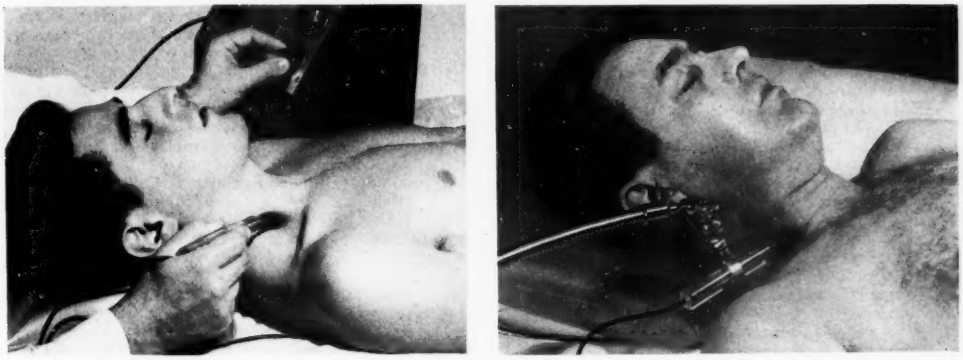


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Fig. 6. a, Use of pen electrode. b, Pen electrode held in place by bedside clamp to maintain effective contact.

In electrophrenic respiration, as in every other form of artificial respiration, the maintenance of a clear airway is a primary consideration.

Both before and since studying the aforementioned series of 24 consecutive subjects, it has occasionally been found that some volunteer has not responded to phrenic nerve stimulation. It is estimated that this occurs about once in each 40 attempts. In such cases, it is not desirable to apply the required threshold amount of current because of increased local cutaneous sensitivity to electrical stimulation. That this was the cause of failure in these instances is indicated by the fact that we have never failed to elicit diaphragmatic breathing in those patients in whom electrophrenic respiration was required as a therapeutic maneuver, except, of course, when axonal degeneration of the phrenic nerve was present.

It cannot, however, be denied that an ectopic phrenic nerve may be the cause of failure in these subjects. From the studies of Rajanna one might expect that this is occasionally the case.

More recently, an attempt has been made to study the possibility of using electrophrenic respiration in newborn infants, using the pen type electrode in preference to the thimble electrode. Although special practice with babies is required to become proficient in this group, effective ventilation can be consistently initiated and maintained.

SUMMARY AND CONCLUSIONS

1. The procedure of phrenic motor point stimulation has been described in detail.

2. It is possible for a trained operator to initiate effective electrophrenic respiration in both adults and infants.

3. The principal requirement in the procedure is the medial displacement of the *clavicular* insertion of the sternocleidomastoid muscle by the exploring electrode.

4. With the patient in the supine position, the head should face forward and be slightly elevated from the table in order to relax the sternocleidomastoid muscle.

5. While pushing the sternocleidomastoid medially, the index finger wearing the thimble electrode or the pen electrode should face posteriorly so as to contact the anterior surface of the anterior scalene at the site where the phrenic nerve is located.

6. It was possible to locate the motor point of the phrenic nerve in 24 volunteers of both sexes. The average "explore" time was 7.4 seconds. The longest time was 45 seconds, and the shortest 2 seconds. In 87 per cent, respiration was started in 10 seconds or less.

7. Electrophrenic respiration can be effectively used in the conventional or modified Schaefer prone pressure position if it is desirable to do so.

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INTRATHORACIC GOITER

Surgical Management and Roentgenographic Appearance

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THE removal of a thyroid tumor from the superior mediastinum is a more difficult technical procedure than the usual thyroidectomy for toxic or nontoxic glandular enlargement. Postoperative complications usually reported in articles on this subject are listed as follows: tracheal collapse, tracheitis, laryngeal obstruction or vocal cord paralysis, hemorrhage, and pulmonary atelectasis (7, 8). Some of the problems encountered in the handling of this type of surgical procedure will be brought into focus by illustrative cases reported herewith.

The roentgenographic anatomy of the superior mediastinum is better appreciated since the introduction and use of angiocardiography in the past decade (25, 26). Angiography has emphasized the major role of the large veins in forming the margins of the silhouettes of the superior mediastinum, both in the normal chest and when a tumor mass is present. Of particular interest in cases with intrathoracic goiter has been the immediate postoperative roentgenographic appearance. The delayed recession in size of the mediastinal silhouette, or occasionally a slight increase in size following surgery even though a large tumor mass has been completely removed, has not been emphasized in the literature on the subject of intrathoracic thyroid tumors. The following illustrative cases were selected to show, among other points, this feature of the delayed recession in size of the mediastinum following the removal of an intrathoracic goiter.

CASE 1. Unit No. 719123. In 1933 this 43 year old woman had a partial thyroidectomy for a nontoxic nodular goiter which had presumably been present for 30 years. In 1943 a second operation was performed for a recurrent mass in the midline. A nodule 1 centimeter in diameter was removed. The pathological report stated that in some places in the specimen small groups and rows of tumor cells were seen scattered in the fibrous tissue as if invading it in a malignant manner. The cells were well differentiated and in no place was blood vessel invasion observed. The pathologist stated: "It is very difficult to decide in this case whether or not this tumor can be considered malignant." The patient was followed at yearly intervals. In 1947 it was noted that her trachea was deviated to the left. There was a palpable mass arising from the thorax on swallowing. Basal metabolism was plus 7 per cent. X-ray examination of the chest revealed evidence of a soft tissue mass in the upper mediastinum interpreted to be a substernal tumor, most likely thyroid (Fig. 1).

On January 12, 1948, the patient had a partial thyroidectomy for a recurrent nontoxic nodular goiter. A 6 by 4 centimeter mass was found in the isthmus adherent to the bony structure of the thoracic inlet, the dome of which protruded above the suprasternal notch. In the anterior mediastinum was a larger mass, 8 by 6 centimeters, extending to the level of the bifurcation of the trachea. Following delivery of the masses a Penrose drain was inserted on the right into the depth of the anterior mediastinum. The pathological findings were interpreted as carcinoma of the thyroid gland (adenoma malignum type).

Her postoperative course was uneventful. She was last seen in April, 1949, at which time there was no evidence of disease in the neck.

CASE 2. Unit No. 934070. This 47 year old salesman was admitted for investigation of a mass in the right upper chest which was found on routine chest x-ray examination. An enlarged thyroid had been present for 9 years. Physical examination revealed a 2 by 3 centimeter mass in the left lobe of the thyroid. Basal metabolism was plus 5 per cent (Fig. 2).

A partial thyroidectomy was performed on December 16, 1948. Both lobes were nodular. Extending downward from the right lobe was a mass 8 centimeters in diameter. The mass reached to the level of the second rib, was adherent to the trachea, and extended into the posterior mediastinum. Following partial removal of the left lobe the mass was removed. A small nodule of loose thyroid tissue in the region of the right lobe was also removed. The pathological report on this nodule was papillary carcinoma. No other evidence of malignancy was noted. A small Penrose drain was inserted into the retrosternal space for drainage.

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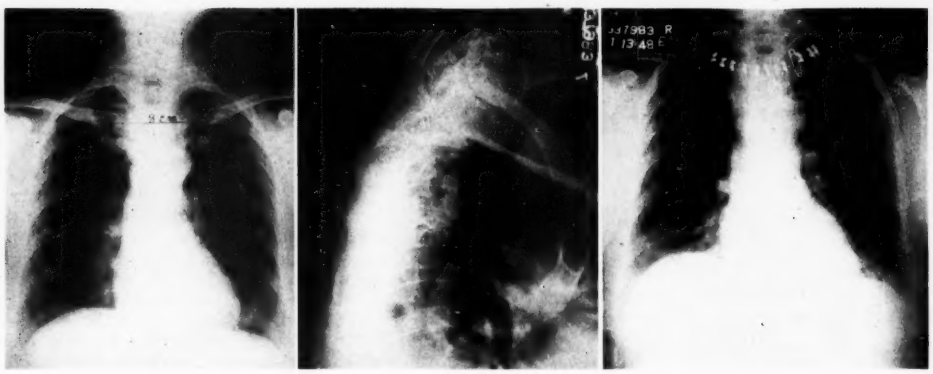

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Fig. 1. Case 1. Unit No. 719123. Roentgenograms of the chest of a 57 year old woman who had a 1 centimeter recurrent nodule removed from the thyroid 4 years earlier, and a partial thyroidectomy for a nodular type of goiter 14 years before film, a, was taken. The superior mediastinum is slightly widened at the level of the clavicles but without lateral displacement of the tracheal air column. A lateral view of the thoracic inlet, b, shows considerable narrowing of the tracheal air column in its anteroposterior diameter, and a slight posterior displacement of the trachea at the level of the clavicles. About 24 hours following the removal of a nodular thyroid mass 6 by 4 centimeters from the isthmus and a larger mass 7 by 6 centimeters from the superior mediastinum which extended down to the level of the bifurcation of the trachea, the chest was re-examined with a bedside x-ray unit, c. The contour of the superior mediastinum is not changed when compared with the preoperative film, a, and there is about the same degree of widening. About 3 months after the third operation, a follow-up roentgenogram of the chest, d, shows a normal contour and size of the superior mediastinum. The transverse dimension has decreased about 2.5 centimeters at the level of the clavicles, and there is a normal contour of the tracheal air column.

After operation there was considerable oozing from the drain site. Twenty-four hours later the patient complained of difficulty in breathing and fullness was found in the wound. Because of progressive dyspnea the patient was returned to the operating room. A considerable amount of blood was evacuated from the wound. The patient was returned to bed in good condition and placed on antibiotics. His temperature subsided to normal on the fifth day. There has been no evidence of recurrent disease.

Case 3. Unit No. 898573. This 49 year old chauffeur was first seen in Vanderbilt Clinic in 1937. He exhibited a mass in the neck and complained of dysphagia. Findings suggested substernal thyroid with tracheal deviation. Basal metabolism rate was plus 23 per cent. He refused operation.

In 1948 blood pressure was 186/106. There were dilated veins in the mass with increase of superficial veins of the left side of the neck and upper chest. His chief complaint was epistaxis. The thyroid gland was diffusely enlarged. The right lobe measured 5 by 8 centimeters, the left 3 by 5 centimeters. There was some increase in retromanubrial dullness to percussion. His sedimentation rate was 94 millimeters per hour. Electrocardiogram showed left axis deviation (Fig. 3).

On February 11, 1948 the patient underwent a partial thyroidectomy. The largest mass of thyroid tissue encountered measured 8 by 7 by 5 centimeters. It contained a considerable amount of calcification particularly in the region which was in contact with the aorta.

By means of blunt dissection and by evacuation of the contents of the tumor a partial removal was effected with some difficulty. A large dead space extended 15 centimeters below the level of the clavicles and for that reason some oxycel gauze and a long strip of fine mesh gauze were packed into the cavity. Approximately 1 hour following his return to the

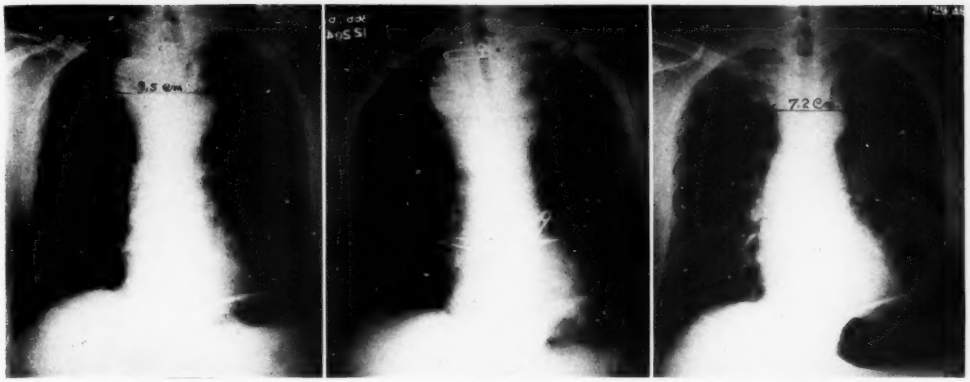

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Fig. 2. Case 2. Unit No. 934070. A 47 year old man had a visible and palpable small thyroid tumor on the left side of his neck for 9 years. A roentgenogram of the chest in postero-anterior projection, a, showed evidence of a rounded tumor in the superior mediastinum extending more to the right than left of the midline. The tracheal air column was slightly narrowed in its transverse diameter and deviated to the left. The day after the removal of the thyroid tumors in both lobes and a larger tumor in the mediastinum which was connected with the right lobe, the operative wound was reopened to relieve pressure on the trachea due to excessive postoperative bleeding. Re-examination of the chest with a roentgenogram, b, taken with the bedside unit the fourth day after the first operation showed the tracheal air column to be in the midline but no appreciable change in size or shape of the silhouette of the superior mediastinum to be present. After an uneventful convalescence, another roentgenogram of the chest, c, which was taken 3 months after the operation showed restitution to normal.

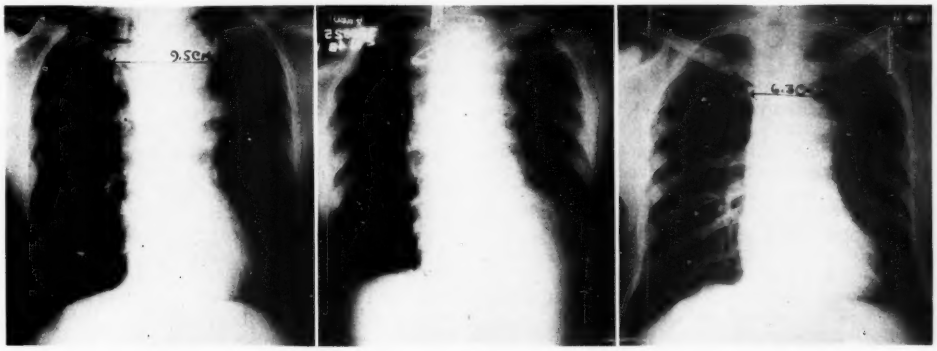

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Fig. 3. Case 3. Unit No. 898573. A 49 year old man had been advised to have an intrathoracic goiter removed in 1937, 9 years before his present admission to the Presbyterian Hospital. Two months before the removal of thyroid tumors (adenomas) from the left lobe of the thyroid and superior mediastinum a roentgenogram of the chest, a, showed a tumor mass extending from the base of the neck to below the level of the aortic arch. The tumor was mainly on the left and displaced the tracheal air column to an extreme lateral position on the right side. Also, considerable calcification was seen in the tumor. (Calcification does not show well in the reproduction). At operation over 200 grams of tumor tissue were removed. The large tumor bed space in the mediastinum was packed with gauze. It was necessary to reopen the operative wound a few hours later to relieve tracheal compression secondary to hemorrhage. Re-examination of the chest with a roentgenogram, b, taken with the bedside x-ray unit 3 days after the initial operation showed about the same degree of widening of the mediastinum and the tracheal air column remaining to the right of the midline. However, the patient was wearing a tracheotomy tube and had the gauze packing in the wound. Another roentgenogram of the chest, c, about 3 months later showed restitution to normal.

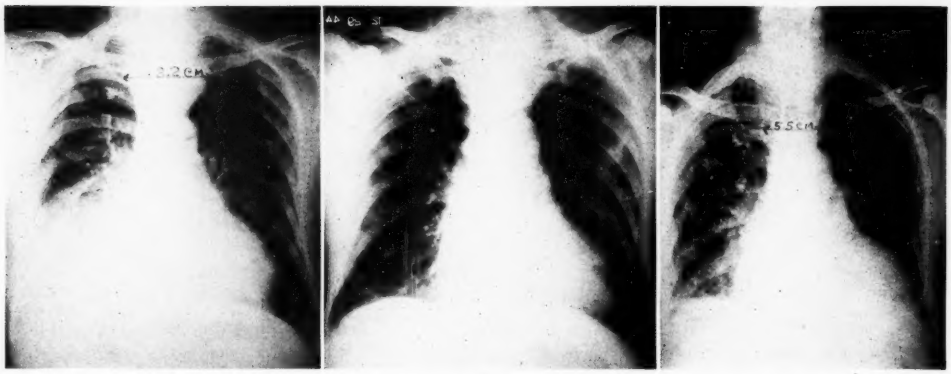

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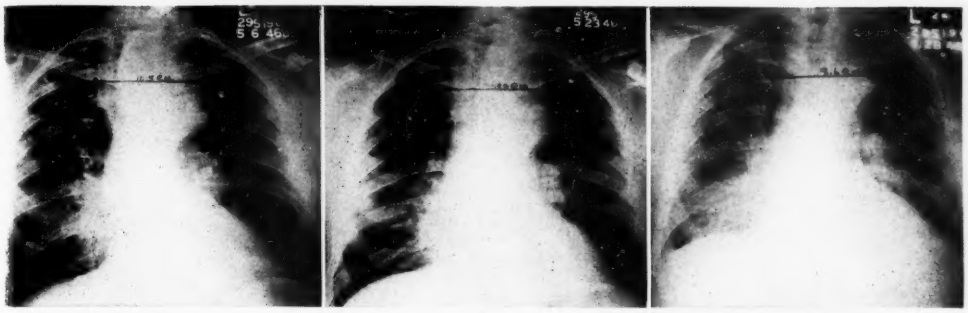
Fig. 4. Case 4. Unit No. 765068. A 65 year old man had been under the care of his local physician for 2 years at which time he was known to have an enlarged thyroid accompanied by auricular fibrillation. When admitted to the Presbyterian Hospital in cardiac failure he had a right pleural effusion. A roentgenogram of the chest, a, showed a tumor mass in the superior mediastinum which displaced the trachea to the right and produced a prominent bulge to the left at the level of the clavicles. At operation a cystic tumor 10 centimeters in diameter was removed from the lower pole of the left lobe of the thyroid. A postoperative roentgenogram of the chest, b, taken on the fifth day showed very little change in the silhouette of the superior mediastinum although the trachea did return to near the midline. A gauze drain still in place in the bed of the tumor mass might have been partly responsible for the trachea not returning to the midline. Re-examination of the chest, c, 5 years after the operative procedure shows about normal contour of the superior mediastinum with the tracheal air column in the midline.

ward the patient exhibited advanced respiratory obstruction. It was noted that his wound was tensely distended. Despite attempts to maintain his airway, with suction through a laryngoscope, complete obstruction occurred within a short period of time. On the ward the wound was hastily opened with a scissors and blood clots evacuated. The muscles were retracted, and at the point of complete obstruction when the patient's pulse had become imperceptible, a tracheotomy was done. His respirations improved on artificial respiration but he was returned to the operating room in a moribund state. A quantity of clotted blood was evacuated from the depths of the mediastinum and the latter packed extensively with oxycel gauze. In the meantime, bleeding appeared to be controlled but when the patient's blood pressure rose as a result of intravenous transfusion, bleeding commenced again. This recurred on several occasions, and it became apparent that control of hemorrhage could not be accomplished by packing alone. During this prolonged period of observation there was a general downward tendency of his blood pressure, varying between 70 and 80 systolic. It became apparent that the sternum would have to be split, and mediastinal exploration done for location of the bleeding point. As this procedure was started the patient's blood pressure became unobtainable and intra-arterial transfusion was started. The sternum was completely split, and the two halves widely retracted. All previous packing was removed, blood clots were aspirated, and a vigorous bleeding point arising from a longitudinal tear in an artery approximately 3 millimeters in diameter was located. It was impossible accurately to identify the artery, which was then ligated. The mediastinum was aspirated, sponged dry, and a loose 2 inch packing was inserted to be brought out the neck. The sternum was closed with No. 28 gauge wire silk and the skin with silk. The entire wound was flooded liberally with sulfamylon-streptomycin solution. His postoperative course was amazingly free of complications. He was discharged to his home on the 17th postoperative day.

CASE 4. Unit No. 765068. This 65 year old salesclerk complained of cough, dyspnea, and orthopnea of increasing severity over a 1 week period. He had been under his local physician's care for auricular fibrillation for the preceding 2 years. Five months prior to admission an x-ray film demonstrated his thyroid to be enlarged substernally. Basal metabolism rate was plus 43 per cent. He was placed on thiouracil with marked relief of symptoms. He was discharged only to be admitted to Presbyterian Hospital in acute cardiac failure 1 week later. Blood pressure was 150/100. His pulse rate on admission was 156. The trachea was markedly deviated to the right (Fig. 4). Findings were consistent with right and left sided failure. Venous pressure was 250 millimeters of water. Electrocardiogram revealed auricular fibrillation. He was rapidly digitalized parentally, given diuretics and a limited salt diet. His basal metabolism rate decreased to plus 11 per cent.

At operation a cyst measuring 10 centimeters in diameter was found at the lower pole of the left lobe with marked displacement of the trachea to the



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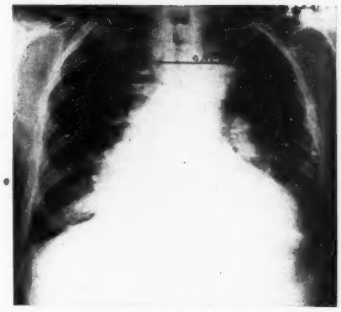

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Fig. 5. Case 5. Unit No. 828122. A 62 year old man with a known thyroid enlargement for 6 or more years was admitted with cardiac decompensation. A roentgenogram of the chest, a, showed a mass in the superior mediastinum projecting above and below the level of the clavicles with its point of greatest width at the level of the first ribs. The tracheal air column was displaced markedly to the right and showed a marked narrowing of its transverse dimension. At fluoroscopy the mass was found to move on swallowing. Also the patient had an enlarged heart. The aorta was dilated and showed an abnormally wide excursion of its walls as seen in cases with aortitis. Re-examination of the chest on the sixth postoperative day, b, after the removal from the posterior mediastinum of a cystic adenoma measuring 7.5 by 11.5 centimeters, showed about the same width of the superior mediastinum at the level of the first ribs but there had been a shift of the trachea to near the midline. The trachea showed some increase in width but had not returned to normal size. Re-examination 1 month after operation, c, showed the trachea to be in its normal position and to have a uniform width of its air column. Also the total width of the mediastinum had decreased but it remained moderately wide. This might have been due to the widened aortic arch. About 11 months following operation and 3 days before death, due to cardiac failure, another examination, d, showed a slight increase in the total width of the superior mediastinum at the level of the first ribs but with a normal appearance of the trachea. The neck veins were engorged and the widening was believed to be due to overdistention of the great veins.

right. After removal of the cyst a cigarette drain was inserted in the left thyroid fossa.

Postoperatively the patient's temperature ranged between 100 and 102.6 degrees. He responded to sulfadiazine administration. Drain was removed on the fifth postoperative day.

The patient has been recently admitted to the urological service where no further evidence of thyroid disease has been noted.

CASE 5. Unit No. 828122. This 62 year old hotel manager was admitted on May 1, 1946, in right and left sided cardiac failure. For 6 years he had been troubled by a "crowing" sound in breathing which was relieved by lying on his right side. He had exhibited symptoms of acute dyspnea, wheezing, and coughing for 1 month. At 25 years of age he had been treated for chancre. Blood pressure was 100/55. His trachea was deviated markedly to the right. A large mass arising behind the left clavicle was palpable on swallowing. Heart was enlarged to the left with sounds of poor quality. Basal metabolism rate was plus 5 per cent. Wassermann reaction was negative.

X-ray films and kymograms of the chest revealed an enlargement of the heart and superior mediastinum (Fig. 5).

On May 17, 1946, following digitalization, a partial thyroidectomy was performed. A mass arising from the lower pole of the left lobe of the thyroid was removed after its contents had been evacuated A Penrose type drain was inserted.

He was discharged with the diagnosis of intrathoracic goiter, aortitis (etiology undetermined) and aortic insufficiency. Serial chest x-ray films were taken over the next 11 months.

He was readmitted 11 months later on March 8, 1947 with a history of increasingly severe attacks of exertional dyspnea in cardiac failure. He expired on April 19, 1947. A postmortem examination revealed luetic aortitis and essentially normal superior mediastinal structures.

CASE 6. Unit No. 885457. A 50 year old widow was admitted with a complaint of progressive enlargement of the neck and hoarseness of 1 year's duration. There had been a more rapid increase in size of a mass in her neck, and a pulling sensation in

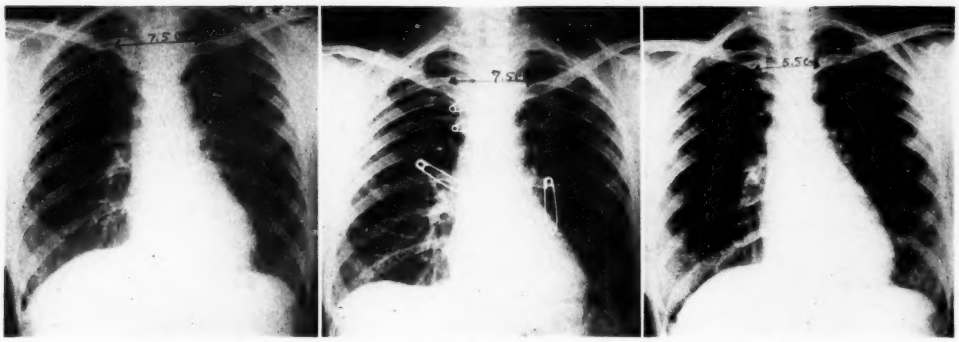

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Fig. 6. Case 6. Unit No. 885457. A roentgenogram of chest, a, of a 50 year old woman showed symmetrical enlargement of the superior mediastinum with about equal degree of widening and with the point of greatest width at the level of the clavicles. The left border was slightly more prominent than the right. The tracheal air column was seen to be sharply deviated to the right above the level of the clavicles and remained to the right of the midline well below the first rib. Re-examination of the chest the second day after the removal of a thyroid adenoma measuring 10 centimeters in diameter from the left lobe of the thyroid, b, showed no appreciable decrease in the size of the superior mediastinum or change in its silhouette. The trachea, however, was found to have returned to the midline. Re-examination, c, of the chest which was made about 3 months after the operation was performed showed about normal contour and size of the superior mediastinum with the trachea in the midline.

the left supraclavicular region for about 2 months prior to admission. On physical examination positive findings were limited to a diffusely enlarged thyroid with substernal extension of the left lower pole. A preoperative examination of the vocal cords revealed some impairment of motion of the left cord on inspiration. There were no signs of toxicity. Basal metabolism rate was minus 2 per cent (Fig. 6).

On December 11, 1947, a partial thyroidectomy was performed, a single large 10 centimeter nodule being removed from the left lobe. The nodule extended several centimeters within the thoracic inlet. It was delivered into the wound and excised behind clamps. The right lobe appeared normal. The wound was closed without drainage. The postoperative course was uneventful save for complaints of shortness of breath. Laryngoscopy on December 17, 1948, 6 months after operation, revealed the return of normal function to the vocal cords.

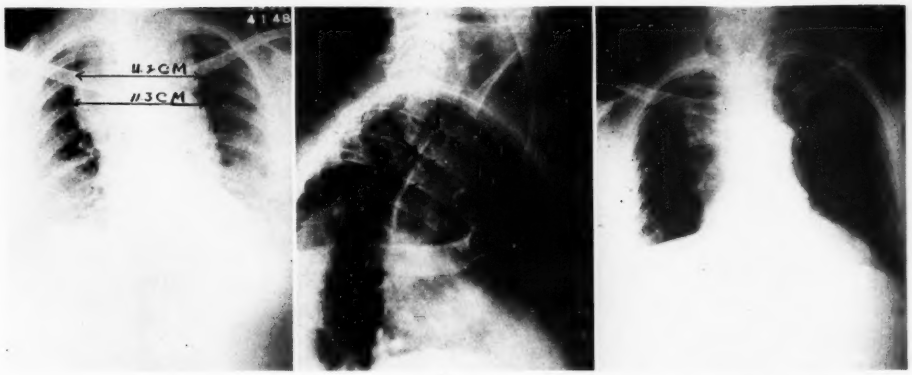
The patient was last seen on October 14, 1948, at which time she had no complaints referable to the thyroidectomy.

Case 7. Unit No. 904621. A 66 year old housewife was admitted on April 5, 1948, with a complaint of slowly enlarging goiter for a period of 15 years, chronic cough for 10 years, and dyspnea for 5 years. In the past 3 or 4 years she noted distended veins over the upper thorax and lower neck. On physical examination she presented a rather tinny voice, obvious stridor, and a large goiter in the neck which rose slightly on swallowing (Fig. 7).

At operation under intratracheal cyclopropane anesthesia the entire gland was a site of extensive cystic and nodular degeneration. The left lobe of the gland measured approximately 16 centimeters from pole to pole. At least 10 centimeters lay below the level of the clavicle and within the superior mediastinum. The trachea was pushed far over to the right in the neck and was markedly compressed in an anteroposterior direction. The right lobe measured approximately 10 by 6 centimeters and extended below the level of the clavicle, for only a short distance. Well down beneath the right lower pole in the posterior mediastinum and apparently separate from the remainder of the gland was another mass of thyroid tissue which was globular in shape and approximately 8 centimeters in diameter The left and right sided masses were easily delivered after the superior and inferior thyroid arteries had been controlled bilaterally. Penrose drains were placed in the depths of the dead spaces and brought out through the muscles at the lateral ends of the wound. Following operation the patient did quite well, running a temperature averaging 102 degrees for 3 days, which gradually declined to normal. Drains and sutures were removed at the end of the second postoperative day. On the third postoperative day a roentgenogram of the chest showed the tracheal air column deviated to the right in about the same position as before operation. There was no decrease in the width of the mediastinum (Fig. 7, c).

The patient was discharged on the ninth postoperative day, her only complaint being a mild cough which was rapidly improving. When seen in June, 1948, she had complete relief of all her symptoms.

Case 8. Unit No. 852730. A 44 year old woman consulted her physician because of stiffness in the neck which began 5 months before admission to this



a b c

d

Fig. 7. Case 7. Unit No. 904621. Examination of the chest, posteroanterior view and oblique lateral views of the thoracic inlet, a and b, of a 66 year old woman with known progressive enlargement of the thyroid over a period of about 15 years showed a marked degree of widening of the superior mediastinum extending well below the clavicles on both sides. The tracheal air column was displaced to the right and posteriorly but considerable tissue was present between the air column and the right border of the mediastinum. The lumen of the trachea was seen to be markedly narrowed in both the lateral and anteroposterior dimensions. On the third postoperative day a roentgenogram, c, showed a slight decrease in the width of the mediastinum and a change in the contours of its borders. The tracheal air column was found only slightly to the right of the midline. Re-examination of the chest about 9 months after operation, d, showed a considerable decrease in the total transverse width of the superior mediastinum but with a soft tissue shadow on the right at the level of the clavicle which might represent some thyroid tissue remaining in the superior mediastinum.

hospital. She was told that she had a tumor in her chest. Radiotherapy given at that time failed to change the size of the lesion. Her only complaint at the time of admission was some shortness of breath on climbing stairs. Physical examination revealed a short, tense female with prominent eyes and a blood pressure of 190/100. There was enlargement of the thyroid with tracheal deviation to the left of the midline (Fig. 8).

On December 24, 1946, a partial thyroidectomy was performed at which time a long pear-shaped, pedunculated, nodular mass which extended some 15 centimeters into the chest was encountered. The mass was delivered by means of curved clamp application to the capsule. The capsule was closed. A Penrose type drain was placed into the depths of the dead space and brought out through the angle of the wound.

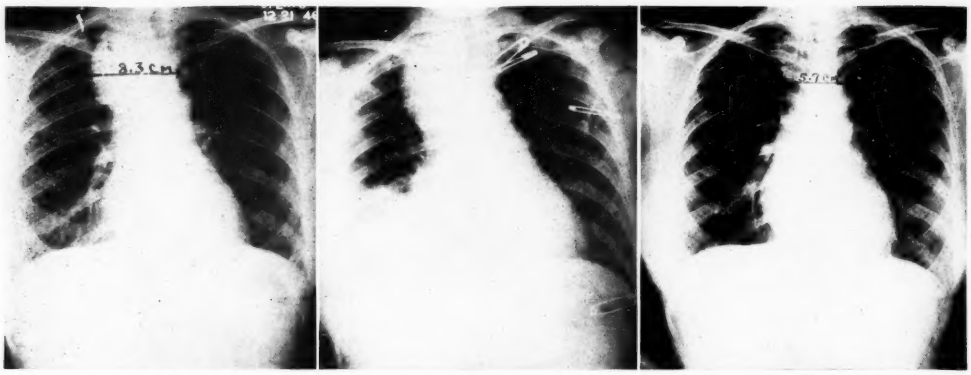
The patient developed physical signs of atelectasis of the right lower lobe on the second postoperative day. She was placed on penicillin and following resolution of the atelectatic process her postoperative course was uncomplicated. She was discharged home on the tenth postoperative day.

She has remained well in the interim.

DISCUSSION

The subject of intrathoracic goiter has been presented in the past by such authorities as Judd, Pemberton, Curtis, Lahey, and Higgins in clear and thorough fashion.

The operative approach to intrathoracic goiter as employed at the Presbyterian Hospital differs little from that described by Judd in 1920. The superior and inferior thyroid vessels are usually controlled from above downward, the strap muscles on either side may be divided and cervical thyroidectomy performed as indicated before delivery of the intrathoracic mass is attempted. The operation from this point has had many modifications, both in our hands and elsewhere, over the course of years according to the preference and the ingenuity of the surgeon. Blunt dissection posteriorly and anteriorly between cervical fascia and the capsule of the gland



a b c

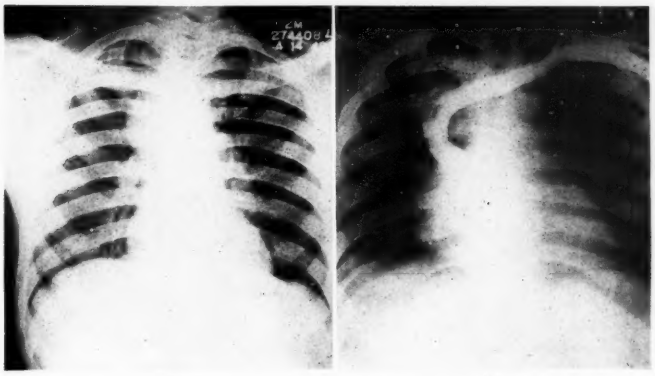
Fig. 8. Case 8. Unit No. 852730. A preoperative roentgenogram of the chest, a, of a 44 year old woman suspected of having a thyroid tumor showed an asymmetrical widening of the superior mediastinum extending down to the level of the second rib anteriorly. The right border projects over the lung field but is sharply delimited and convex. The trachea was found deviated to the left of the midline. Re-examination on the second day after a thyroid tumor of mass 15 centimeters in diameter was removed, b, showed essentially the same degree of widening of the mediastinum and no appreciable change in its silhouette, although the trachea had returned to near the midline. A transient atelectasis of the right lower lobe was present. Two years after operation, a roentgenogram of the chest, c, showed the mediastinum to have about normal appearance with the tracheal air column in the midline.

has been usually employed, thus avoiding a possible vacuum created on attempt at removal of the intrathoracic mass. This is followed by some method of delivering the larger pliable diameter of the mass through the fixed and narrower thoracic inlet. Morcellization, fragmentation, curetting, aspiration of the contents, special retractors, spoons, thyroid hooks, and clamps have been tried in different cases. Our preference as described by us in 1941 (W.B.P.) has been to remove some of the contents of the intrathoracic goiter and then to deliver it by carefully placing a series of curved clamps along the capsule of the tumor under direct vision, guided by the operator's fingers also placed within and without the capsule. In this fashion one may carefully work around the capsule of the tumor delivering it gradually as each new clamp is applied until the entire mass has been delivered.

Since it is known that the blood supply travels downward from the inferior thyroid arteries as the tumor grows into the thorax, the problem of hemorrhage, once these vessels have been controlled, is usually not a great one. Blunt dissection is usually safe, although in the large intrathoracic type, adherence to the surrounding tissues of the mediastinum may make this an extremely dangerous procedure.

We have found it necessary to split the sternum only rarely in any of our cases to remove the tumor from the mediastinum. However, in Case 3, postoperative tracheotomy and sternum splitting, as well as heroic intravenous and intra-arterial support were required for control of serious hemorrhage. In retrospect, we feel that sternotomy or thoracotomy allowing for complete visualization and mobilization of the tumor with ligation of the aberrant vessel causing the hemorrhage might have been the procedure of choice. The authors are cognizant of the combined chest and cervical approach recommended by Sweet for posterior mediastinal thyroid tumors. We have recently encountered several cases of posterior mediastinal thyroid tumor requiring this approach. We have not encountered cases of aberrant mediastinal goiter, similar to those reviewed by Rives in his discussion of this syndrome in 1947. None of the cases presented here could be called complete intrathoracic goiter according to the classification of Curtis.

That there are theoretical objections to fragmentation of the intrathoracic mass before removal cannot be denied. The possibility exists of leaving fragments of tissue behind and in Case 1 and Case 2 in which malignant



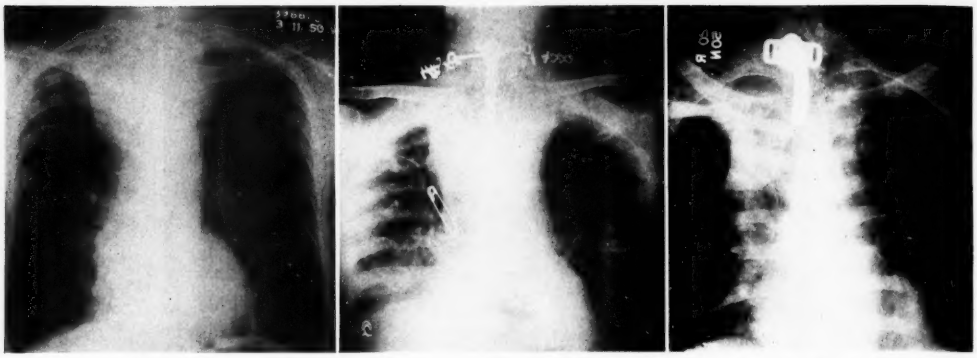
a b

Fig. 9. A roentgenogram of the chest in posteroanterior view taken of an 18 year old negro male showing a tumor mass in the superior mediastinum, a. Exploration and histological section of the mass showed it to be sarcoidosis. A roentgenogram taken within the first second following the injection of 70 per cent diodrast into the left antecubital vein, b, shows the position of the superior vena cava in relation to the mass in the anterior and superior mediastinum. This case illustrates the marginal position of the large veins in the mediastinal silhouette as compared with the arteries shown in Figure 10.

disease was demonstrated in postoperative microscopic examination, we feel that fragmentation and piecemeal removal is questionable cancer surgery. Fortunately, the incidence of cancer in intrathoracic goiter is low. Of 542 cases of intrathoracic goiter reported by Pemberton, 7 or slightly over 1 per cent showed malignant change. In Case 2 the tiny nodule was the only evidence of cancer noted. In Case 1 the previous history of tumor was a clue to the existence of recurrent malignant disease. It would seem that in cases similar to the latter it would be wiser to anticipate such a contingency by use of sternotomy for wider exposure and removal of the tumor *in toto*.

Once the tumor has been delivered from the mediastinum there is no general agreement as to the best method of handling the residual cavity. In selected cases some surgeons have used no drainage. This has also been our practice in the smaller "substernal" or incomplete intrathoracic (Curtis) tumors, when hemostasis has been satisfactory. King has described a method of complete hemostasis by placing a series of continuous purse-string sutures superficially in the cervical fascia surrounding the tumor, taking care to avoid piercing the pleura or vessels. "In using this technique little or no drainage is necessary and no more serum is found than in the ordinary goiter." Others have preferred to use

Fig. 10. A roentgenogram of the great vessels taken within 0.5 second after the retrograde injection of 35 per cent diodrast into the left carotid artery in a normal patient who was suspected of having an anomaly of the great vessels. It is used to compare with Figure 9 to show that the arteries lie mesial to the large veins and are less likely to contribute to the margin of the mediastinal silhouette in the pressure of an intrathoracic nonvascular tumor.



a b c

Fig. 11. A roentgenogram of the chest, a, on a 75 year old male, Unit No. 988802, before an emergency operation had to be done to relieve respiratory distress. The markedly widened mediastinum and narrowed tracheal air column, which was deviated slightly to the right, was produced by a large intrathoracic goiter. Re-examination of the chest, b, with the bedside x-ray unit on the first postoperative day showed no reduction in the size of the mediastinum. The patient was wearing a tracheotomy tube, and a single Penrose drain was left in the space occupied by the large tumor mass. A venogram, c, was done on the fifth postoperative day to show the anatomical position of the superior vena cava relative to the margin of the superior mediastinum. All drains had been removed when the venogram was done. The usual location of the great veins in relation to the margin of the mediastinal silhouette, when a tumor is present, is emphasized in this postoperative roentgenogram.

a small Penrose drain for a few days. At the other extreme, both Lahey and Cattell, based on their voluminous experiences with thyroid surgery at the Lahey Clinic, have repeatedly stressed the necessity of lightly packing the cavity remaining behind and have advised leaving this packing in place for 1 to 3 weeks. Lahey has written, "We have had the unfortunate experience of removing the drain at the end of the fifth or sixth day, failing to put back an adequate drain, seeing the wound heal by first intention, and sending the patient home only to have her return within the week or ten days with the accumulation of a large amount of fluid in the unobliterated mediastinal cavity." The decision to drain or not to drain is, in our opinion, one of relative degree, depending on the size of the dead space, hemostasis, contamination of the mediastinum with bits of potentially necrotic thyroid tissue and a desire to avoid pressure symptoms from collected serum, edema, etc. We have not encountered the problem of uncontrolled mediastinitis in these cases. We feel that prophylactic drainage for prevention of mediastinitis in this age of antibiotics and sulfa drugs has been overemphasized and that the practice of leaving a drain in the mediastinum for weeks in a clean case is not advisable. Our own preference has been to drain the majority of these cases for a few days, usually with one or two Penrose drains brought out the lateral angle of the wound. Only rarely have we resorted to extensive packing. In the smaller glands we have preferred not to drain. It is significant that the hemorrhage in Case 3 already referred to, was controlled by packing of the mediastinal cavity during the period of hypotension, but the packing of the deep cavity was ineffectual in controlling hemorrhage when the blood pressure was restored to more normal levels. In this case a large amount of oxycel gauze in addition to continuous gauze packing was employed. It is obvious that packing of the mediastinum is not to be preferred over ligation in the control of bleeding from an artery of the size encountered. Herbert C. Maier has called our attention to the fact that drainage of a large intrathoracic space in which pleura has been torn may result in a fatal tension pneumothorax. George Humphreys has advocated deliberately opening the pleura in cases in which a dead space of any size is left, then taking pains to make an air tight closure in the neck. This conforms with the practice of other thoracic surgeons in dealing with resection of

mediastinal tumors, namely deliberately to leave an opening in the mediastinal pleura so that fluid will escape into the pleural cavity where it absorbs rapidly or can be tapped.

Curtis and Cattell presented evidence as to the usual fate of the trachea following surgery for removal of intrathoracic goiter, showing by means of postoperative chest roentgenograms that the trachea, deviated preoperatively, had approached the midline by 3 months postoperatively.

Cattell in the discussion of drainage of these mediastinal cavities stated: "In the absence of such drainage we have seen serum accumulate in such a pocket sufficient to produce as great a tracheal deviation as was caused by the goiter. X-rays taken with the packs in place will show little, if any, diminution in the size of the cavity immediately postoperatively and there is slight if any return of the trachea at this time." Case 7 of our series in which mediastinal packing was used for a short period was the only example which we were able to find among our cases not exhibiting almost immediate return of the trachea in direction of normal. Persistent tracheal deviation suggests residual tumor mass.

Others have noted the tendency of the mediastinal cavity to fill with accumulated blood and lymph in the postoperative period. Prioleau includes in his article reproductions of roentgenograms showing an excellent example of the postoperative collection and its subsequent subsidence. Part of the shadow seen by roentgenographic studies in these and similar cases may result from subpleural edema, sometimes interpreted as fluid, seen in postoperative chest films following removal of segments of lungs.

Mora and Isaacs in 1944 reported a case of posterior mediastinal goiter, drained for 48 hours, with a smooth postoperative recovery with a roentgenogram of the chest taken 1 month postoperatively showing the mass to be approximately one-half the size of the preoperative dimensions. Reference to this same phenomenon was made by Wallace in 1945 who reported a case of intrathoracic goiter treated by surgery without drainage. "Some fluid probably accumulated in the cavity left by the mediastinal mass. Serial x-ray films showed that spontaneous resolution occurred. No deleterious effects were noted."

The superior mediastinum remains widened for some time after the removal of a tumor mass. Our personal observations on serial films of the chest suggest that it requires from 6 to 12 weeks for restitution to normal. The persistent widening appears to be due in part to the presence of edema and possibly slight hemorrhage in some cases. Edema alone would not be likely to persist more than 2 weeks. The silhouette of the mediastinum is greatly influenced by the degree of positive pressure exerted upon it by the expanded lungs. This molding effect of the lungs is produced gradually but effectively. It is probable that the apparent lag in restitution to normal of the mediastinal silhouette is dependent upon the molding effect of the expanded lungs rather than persistence of edema or hemorrhage.

SUMMARY

The management of a selected group of patients with intrathoracic goiter is presented to illustrate the surgical features usually encountered.

An apparent lag in the restitution of the mediastinum to normal after the removal of a tumor is probably due to the presence of edema and, in some instances, hemorrhage. The final molding effect to produce a normal silhouette is probably dependent upon the positive pressure exerted by the expanded lungs.

The position of the large veins in the lateral borders of the mediastinal silhouette in contrast to the more centrally located arteries is emphasized by angiograms.

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THE SURGICAL SIGNIFICANCE OF SMALL BOWEL TUMORS

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THE recognition of small bowel tumors parallels the growth of roentgenology. During the past few years, these lesions have aroused an increasing interest; their frequency seems to be on the increase. Small bowel tumors are found more frequently today because more thorough examination by roentgenologists is possible. In spite of the fact that the small intestine constitutes 75 per cent of the alimentary tract, tumors of this part of the bowel are uncommon. Morison states that "for the area exposed, the small intestine enjoys as great an immunity from new-growth as any part of the body." This is an interesting observation since the small bowel follows the stomach and precedes the colon, which two areas are the seat of over 40 per cent of all malignant growths.

Shallow, Eger, and Carty, in a collected series of 137,174 autopsies, found approximately 36 carcinomas of the large intestine to one carcinoma of the small intestine. Fraser of Glasgow, Raiford of Johns Hopkins, and Buckstein of Bellevue Hospital reported a similar rare incidence. C. W. Mayo (7) reported 108 malignant tumors of the small bowel between 1907 and 1939 at the Mayo Clinic. In the same period of time, Weber and Kirklin reported 41 benign lesions of the small bowel from that institution.

In the past, most small bowel tumors have been diagnosed late in the course of the disease. It is hoped that this study will focus attention upon the early symptoms, physical, and x-ray findings, and pertinent laboratory data so that the diagnosis may be established at an earlier date.

This study deals with 16 tumors of the jejunum and ileum. The most common tumor of the small bowel is carcinoma. Cameron, in reporting 200 collected cases of small bowel malignancy, found carcinoma in 109, sarcoma in 78, and carcinoid tumors in 13. He noted that sarcoma and carcinoid tumors of the small bowel may be multiple. Carcinoma occurs more frequently in the jejunum. Sarcoma and carcinoid tumors are found more frequently in the ileum.

Metastatic involvement is a frequent finding. In 11 of the 14 malignant tumors in this series, metastatic spread was evident. Distant metastases are uncommon. The metastatic involvement within the abdomen may be extensive.

Benign tumors of the small bowel occur less frequently than do malignant tumors. Benign tumors arise from any of the cellular elements of the bowel wall. In this series of 16 cases 2 were benign; the tumors being fibroma and leiomyoma, respectively, and both tumors were in the lower ileum.

SYMPTOMS

A marked loss in weight was the most common presenting complaint, occurring in 14 of the 16 cases or in 87.50 per cent. A loss of from 8 to 30 pounds in 6 to 8 months occurred in all 14 cases of malignancy.

Recurring episodes of partial intestinal obstruction were present in 14 of the 16 cases, or 87.50 per cent. These episodes manifest themselves by pain and abdominal cramps. Nausea and vomiting occurred in 10 of the 16 cases, or 62.50 per cent. Diarrhea is a less common symptom, being present in 3 of the 16 cases, or 18.75 per cent. These episodes occur at varying intervals of 3 to 4 months. Each attack is more severe than the preceding one. The pain is usually periumbilical. It may occur long before bleeding or obstruction. Acute obstruction may be the first symptom in poly-

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Fig. 1. Recumbent flat plate of abdomen showing dilated loops of small bowel. The obstruction was due to a fibroma of the ileum with intussusception (Case 5).

Fig. 3. Segmental spasm of small bowel suggesting disturbed motility. The lesion causing this segmentation was a mucoid carcinoma of ileum (Case 2).

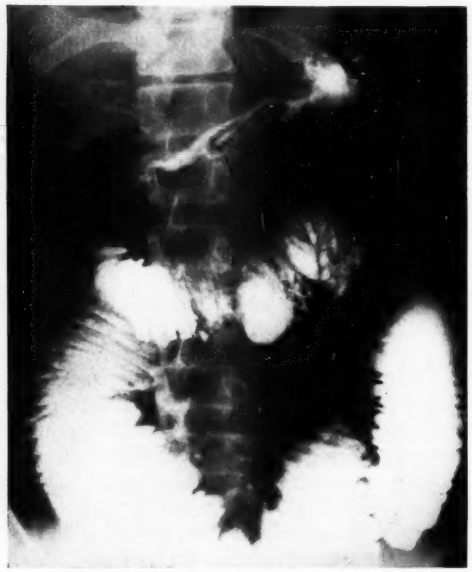

Fig. 2. Dilatation of jejunum with area of constriction due to adenocarcinoma.

poid benign or malignant tumors. Two of this series of 16 cases had dramatic episodes of intussusception. In an adult, intussusception of the small bowel is frequently precipitated by a tumor.

PHYSICAL FINDINGS

Distention of the abdomen, suggesting a partial intestinal obstruction, was present in

TABLE I.—TUMORS OF JEJUNUM AND ILEUM

Carcinoma	
Adenocarcinoma of jejunum	2
Papillary adenocarcinoma of jejunum	1
Adenocarcinoma of ileum	2
Mucoid carcinoma of ileum	1
Sarcoma	
Lymphosarcoma of ileum	2
Spindle cell sarcoma of ileum	1
Myosarcoma of ileum	1
Myeloblastic sarcoma of ileum	1
Carcinoid tumors of ileum	3
Benign tumors	
Fibroma of ileum	1
Leiomyoma of ileum	1
	16

Fig. 4. Adenocarcinoma of jejunum producing partial obstruction (Case 1).

Fig. 6. Mucoid carcinoma of lower ileum in 53 year old female (Case 2).

10 of 16 cases, or 62.50 per cent. Associated with the distention, hyperperistalsis was noted.

Acute intestinal obstruction was present in 4 cases, or 25 per cent, at the time of admission to St. Luke's Hospital.

Anemia of severe degree was present in 10 cases, or 62.50 per cent. Gross hemorrhage, which produced a shock syndrome, was present in 1 case. Four patients had tarry stools. The 5 remaining cases producing anemia gave no history of blood loss. Mayo and Nettrour (8) state that 5 of their series of 31 cases of carcinoma of the small bowel had been treated for anemia without success.

A palpable mass in the abdomen was found in 5 cases, or 31.25 per cent. In Cameron's series of 200 cases, 65 per cent of the sarcomas and 29 per cent of the carcinomas were palpable in the abdomen. Pelvic examination is essential. Three tumors in our series of 16 cases were found on pelvic examination.

X-RAY FINDINGS

Careful small bowel x-ray studies are necessary to establish the diagnosis of small bowel

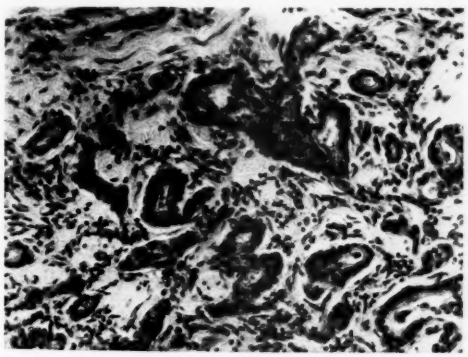

Fig. 5. Photomicrograph of section of an adenocarcinoma of jejunum. Masses of atypical glandular epithelium were present invading the fibroblastic tissues of the wall of the bowel.

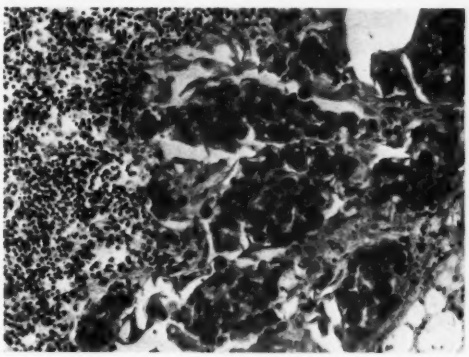

Fig. 7. Photomicrograph of section of a mucoid carcinoma of lower ileum. Masses of carcinoma cells with mucoid degeneration and no discernible glandular arrangement, invading the bowel wall.

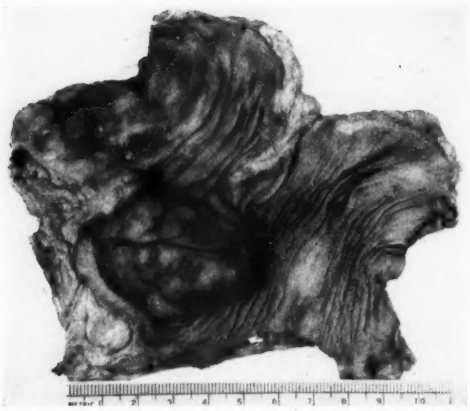

Fig. 8. Hemorrhagic myosarcoma of the ileum producing bloody stools and intussusception (Case 3).

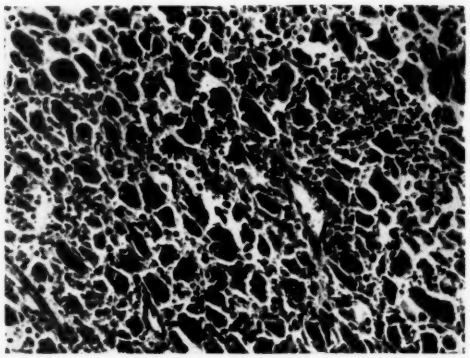

Fig. 9. Photomicrograph of a section of a hemorrhagic myosarcoma of the ileum. Large and medium-sized cells with acidophilic cytoplasm and one or more large vesicular nuclei. Interspersed are groups and isolated long spindle shaped cells, some of which are in mitoses (Case 3).

tumors. Small bowel x-ray studies must be individualized. These tumors are frequently overlooked in the routine gastrointestinal x-ray examination. Scout films with patients in the recumbent and upright positions are important as a preliminary study, as emphasized by Jenkinson, Pfisterer, and Seitz (Fig. 1).

A dilatation proximal to an area of constriction is a common finding (Fig. 2). Retention of barium in the small bowel for a period of more than 8 hours is suggestive of a lesion. Frequently segmentation of the barium occurs in the small bowel (Fig. 3). This observation suggests disturbed motility and merits further investigation.

PATHOLOGY (TABLE I)

In 6 of the 16 cases, or 37.50 per cent, carcinomas were present. Three tumors were in the jejunum and 3 were in the ileum. All of the carcinomas, except 1, were annular and constricting the bowel lumen. In every case, metastatic spread was noted.

CASE 1. *Adenocarcinoma of the jejunum.* J. D., a 56 year old white male, was admitted to St. Luke's Hospital January 19, 1947. He gave a history of severe generalized abdominal pain following the intake of food, with nausea, vomiting, and gaseous distention, of 2 months' duration. There had been a 30 pound loss of weight. At operation, an annular carcinoma of the jejunum was found and resected (Figs. 4 and 5). Three months later he had a recurrence of the obstruction and widespread metastases were present.

CASE 2. *Mucoid carcinoma of the ileum.* T. C., a 53 year old white female, entered St. Luke's Hospital January 10, 1946. She complained of upper abdominal pain of 11 weeks' duration, with no nausea or vomiting. A mass the size of a grapefruit was palpable below the umbilicus (Figs. 6 and 7). At operation a tumor of the ileum was resected. An end-to-side ileotransverse colostomy was performed. Meta-

Fig. 10. Multiple carcinoid tumors of ileum (Case 4).

static carcinoma was present in the regional lymph nodes.

She was admitted 2 years later with a recurrent tumor. At operation a metastatic carcinoma, the so-called Krukenberg tumor, was found in both ovaries. At the present time patient is working as a ticket agent at an elevated station in Chicago.

Five cases, or 31.20 per cent, were sarcomas. All the tumors were in the ileum. Four of the 5 tumors were extraluminal and nonobstructive. Inflammatory adhesions to surrounding structures was a characteristic finding. Intra-abdominal metastases were present in 2 cases.

CASE 3. *Fungating hemorrhagic myosarcoma.* E. O., a 70 year old white female, entered St. Luke's Hospital in October, 1939. She complained of severe umbilical pain, nausea, vomiting, blood in the stool, and a loss of 30 pounds in weight. She gave a history of two similar attacks of partial obstruction in the previous 3 months. A flat x-ray film taken elsewhere showed the signs of a small bowel obstruction. At operation an intussusception of the ileum was found 4 feet from the ileocecal junction. It was secondary to a myosarcoma (Figs. 8 and 9).

Three tumors, or 18.70 per cent, were carcinoid tumors. All the tumors were in the ileum. In the ileum, carcinoid tumors are frequently multiple and malignant (3, 6). Metastatic spread to the regional lymph nodes was found in the 3 cases.

CASE 4. *Carcinoid of the ileum.* L. G., a 45 year old white female, had been hospitalized 3 times since August 1948. On the first admission a nephrectomy was done for a pyelonephritis, with a staghorn calculus. Ten months later she had a vaginal hysterectomy. Nine months later she was admitted because of intermittent left flank pain. Orthopedic, urologic, and gastrointestinal studies were negative. The complaints persisted and she was again hospitalized in 4 months. During her hospital stay, she developed nausea, vomiting, and localization of the pain in the lower left mid-abdomen. X-ray study of the small bowel showed a moderately dilated lower ileum with areas of segmental spasm.

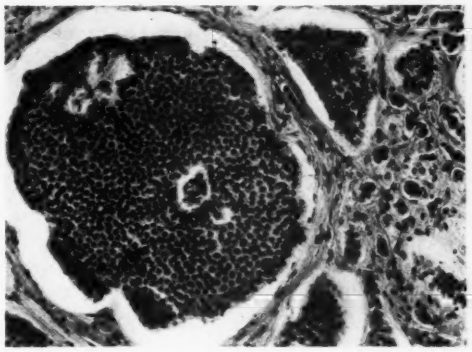

Fig. 11. Photomicrograph of section of regional lymph node. Lymph node metastases from carcinoid tumor of the ileum. Large and small masses and cords of cells of medium size. The cells have granular cytoplasm and large vesicular nuclei and chromatin granules (Case 4).

At operation multiple carcinoid tumors of the terminal ileum were found (Figs. 10 and 11). A long segment of ileum was resected. Metastatic lymph nodes were removed at the base of the mesentery. No liver metastases were noted. The patient is living and well with no recurrence 2 years after surgery.

Two tumors, or 12.50 per cent, were benign. Both tumors were in the ileum, one a fibroma and the other a leiomyoma.

Fig. 12. Fibroma of ileum which produced intermittent obstruction and subsequent intussusception.

CASE 5. *Fibroma.* A. V., a 54 year old white female, entered St. Luke's Hospital, September 10, 1948. She gave a history of vomiting, generalized pain, and belching of 3 weeks' duration. The abdomen was distended and the bowel sounds were audible across the room. A flat x-ray film showed evidence of marked dilatation of the jejunum, a sign of small bowel obstruction. Suction with a Miller-Abbott tube effectively decompressed the small bowel. The symptoms recurred and exploratory laparotomy was performed. An intussusception which included 12 inches of the proximal ileum was resected (Fig. 12). The tumor was a huge submucous fibroma. Recovery was uneventful.

Fibroma of the small bowel is rare. Thirty-four cases have been reported.

Thirteen of the 16 tumors in this series were located in the ileum, 3 in the jejunum.

OPERABILITY AND PROGNOSIS

In the 14 malignant tumors, 9 were explored and 8 lesions were resected. Five tumors were found at autopsy. Three patients in whom the tumors were resected are well, with no evidence of recurrence after 8, 3, and 1 year, respectively. Three patients survived surgery but died within a few months of recurrence. In 1 case the tumor was resected, and a recurrence developed 2 years later. A secondary operation was performed and patient is living 3 years following resection of the recurrence.

Radical resection was carried out in 64 per cent of Cameron's 200 collected cases. Mayo's series in 1940 had a 42.4 per cent resectability rate.

Early recurrence within a few weeks to 2 years may be expected unless thorough removal of regional lymph nodes is done. The average duration of life in Cameron's collected cases was 17.6 months following the resection. In Mayo and Nettrour's 31 cases of jejunal carcinoma, 2 patients survived for a period of 7 years.

In carcinoid tumors (3), however, the grade of malignancy is low. Remarkably long survival periods have been reported despite the presence of extensive and distant metastases at the time of surgery.

SUMMARY AND CONCLUSIONS

1. The symptoms, findings, and operative results in 16 cases of tumors of the ileum and jejunum are presented. This study was carried out with the hope that more early diagnoses will be made.

2. Delay in diagnosis occurs frequently and can be attributed to the vague symptoms manifested by these tumors. This is particularly true in the presence of gall stones or peptic ulcer, the symptoms of which closely resemble those of tumors of the small intestine.

3. Episodes of abdominal cramps, nausea and vomiting, weight loss, and anemia are indications for thorough x-ray studies of the small bowel.

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TOTAL SPINAL ANESTHESIA IN THE SURGICAL MANAGEMENT OF A CONGENITAL ARTERIOVENOUS ANEURYSM

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THE most hazardous lesion technically which confronts the neurological surgeon is the congenital arteriovenous aneurysm. Because of the supreme risks and extreme dangers attending the attempted radical removal of these anomalies, even the most intrepid neurosurgeons have in the past (1) considered them as inoperable. In recent years newer hemostatic methods and more exact delineation of the lesions by means of cerebral arteriography have made possible a more courageous attack upon these vascular tumors. Nevertheless, they still remain exceedingly formidable problems and one must utilize every possible surgical adjunct to minimize the operative risks. These basically, in the plexiform angiomas, would be any aid that would reduce the hemorrhagic possibilities.

It is feasible to extirpate totally this type of vascular malformation without disabling neurological sequelae. This has been demonstrated by the reports in the literature (6, 7, 8, 9). Olivecrona, to whom credit should be given for the first successful removal, has attacked 43 such vascular maldevelopments with an operative mortality of only 9.3 per cent. This is a striking tribute to his surgical courage and skill but, as he warns the uninitiated, the extreme risk of massive hemorrhage which frequently accompanies the radical removal of these aneurysms is the stymie.

In spite of the tremendous technical difficulties encountered in these vascular masses, the consensus of ideas of previous authors has been that one is justified in selected cases in assuming the operative risk in the attempt to reverse an otherwise hopeless situation.

One of us (H.S.S.) having personally experienced the varied and formidable surgical technical problems presented in the radical extirpation of 8 cerebral arteriovenous aneurysms, the authors have sought some method of simplifying the surgical attack on these cerebral blood vessel masses. Although there were no operative mortalities in this small group, 3 of the cases were complicated at some time during the operative procedure by almost uncontrollable bleeding. Two of these experiences temporarily appeared to warrant abandonment of the surgical efforts. Our personal experiences have been those of all previous authors on this subject; namely, the problem of blood loss has been the paramount hazard in the operative attack. All the various measures which have been recommended as adjuncts in minimizing the severe exsanguination which has so often defined one's efforts at total excision have been considered and most of them have been given a trial. In one instance, the method reported by Gardner was attempted without success. The blood pressure in this case was maintained well below shock levels but the uncontrollable bleeding continued until all the contributing arteries had been ligated. In this experience there appeared to have been no worthy technical help in competing with the hemorrhage from the tumor in spite of this phlebotomy. One of us (E.F.F.) in 1949 witnessed an operation, under total spinal anesthesia, on Professor Learmonth's service at the Royal Infirmary in Edinburgh. Following a review of the physiological responses in the use of this cadaveric surgical venture (10) the possibilities of its utilization as a valuable help in the surgical attack on these massive cerebral vascular growths suggested itself. With due consideration for the possible complications and having no precedents as a guide, it was planned to subject a suitable selected urgency to this type of spinal anesthesia; this, in the hope of modifying the surgical hazards of the

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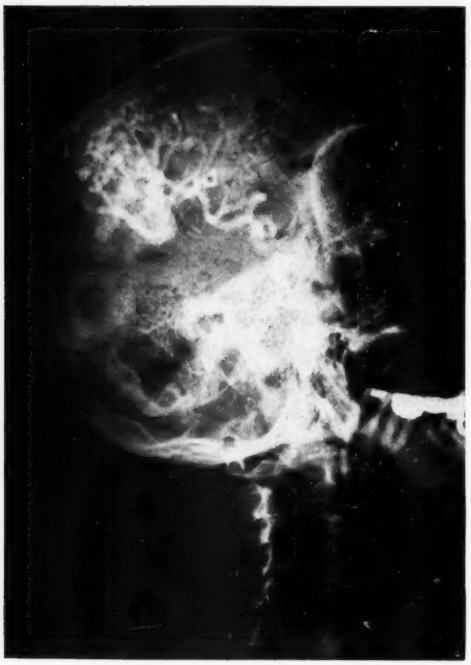


Fig. 1. Preoperative arteriogram demonstrating the location and extent of lesion.

past experiences in these particular craniotomies. The following case is a report of this experience. It suggests the potentialities of this method of anesthesia as a support in the technical competition of these formidable neurosurgical problems. Perhaps with this added help, even in the hands of the less surgically experienced, neurosurgical fatalities may be minimized.

C.K. (L.V. Hospital no. 28545), a 52 year old white male was admitted to the hospital November 7, 1950. He gave a history of uncontrollable jacksonian convulsions for a period of 25 years and a 2 year story of a progressive paralysis of the left extremities, the latter to the degree that he had a disability which made locomotion without support difficult. There had occurred a progressive deterioration of his mental faculties. The focal seizures, even on large doses of anticonvulsants, had been occurring as frequently as ten per day. These involved the left arm primarily but on occasions the left leg as well. He had had only four major seizures during the 25 year period. Unilateral headaches were frequent and a disabling accompaniment. At no time from the onset of symptoms did he describe symptoms suggesting any cerebral or subarachnoid hemorrhage. He had previously engaged in a responsible position, but, in a 2 year period, he had deteriorated mentally to such a level that he was unable to maintain a self-supporting economic status.

Positive neurological findings. The patient was a well developed, muscular white man; there were no evidences of skeletal or muscular growth asymmetry. He exhibited no angiomatous skin blemishes. A cranial bruit was not heard subjectively or objectively. He was markedly depressed mentally. He demonstrated preservation of normal memory but there was an obvious sluggishness in cerebration. This, in the nature of a slowing of intellect and a negativistic personality. Two focal convulsive seizures involving the left arm and hand with transient spread to the left foot and shoulder were observed during the initial neurologic examination. He had no evidence of increased intracranial pressure. There were no objective cranial nerve disturbances noted. The left hand grip was weak. He had marked awkwardness in the performance of intricate functions of the left hand and fingers. The muscle tone was increased and there was exaggeration of the deep reflexes in the two left extremities. The gait was typically hemiplegic on the left. Sensory examination revealed no disturbances of these modalities. Visual range was normal. The routine blood studies were normal. There was no evidence of polycythemia. The Wassermann reaction was negative. Roentgenograms of the skull were found to be within normal limits.

Pneumoencephalography depicted a diffuse cortical atrophy with a greater enlargement of the left lateral ventricle but with no evidence of displacement of the ventricular system.

A right percutaneous carotid arteriogram performed immediately following the pneumoencephalogram (Fig. 1) outlined a massive arteriovenous aneurysm involving the entire right parietal lobe. On the anteroposterior positions this contrast study depicted the lesion to be situated deep within the hemisphere, near the midline, being supplied by arterial branches from both the anterior and middle cerebral arteries. The left carotid arteriogram excluded the presence of a similar lesion on the left. This contralateral injection more accurately established the anterior cerebral artery supply of the aneurysm. The vascular studies demonstrated the paucity of filling of the normal cerebral arteries bilaterally. These confirmed the concepts of Olivecrona, "that in these arteriovenous communications the blood from both cerebral hemispheres is short-circuited, being literally sucked into the aneurysm to produce deficient circulation to normal areas of the involved side as well as to the opposite hemisphere."

Operations. Because of the uncontrollable convulsive seizures and the progressive neurological handicaps, the patient expressed a wish that some effort be made to salvage him. With the lesion in the

parietal lobe of the nondominant hemisphere and in view of the advanced degree of hemiparesis, it was felt that if a total removal could be accomplished, no new neurological handicaps would result. The magnitude of the lesion demonstrated in the arteriograms certainly offered extreme surgical dangers and it appeared that the surgical risks under conventional anesthesia were somewhat prohibitive. The mortality and morbidity of spinal anesthesia were discussed with the patient and since his existence was such as to make life undesirable, he willingly accepted the venture. In order to reduce the operative time spent in attacking the lesion, the operation was planned in stages. The initial craniotomy exposure was performed as a primary stage under pentothal and novocain anesthesia. The cortical cerebral changes as characteristically seen in massive arteriovenous communications were those illustrated in Figure 2. When the magnitude of the lesion had been evaluated and the surgical attack planned, the dura was closed, the bone flap replaced, and a primary layer closure of the wound was effected. The patient suffered no upsets from this initial osteoplastic exposure.

Two days later the wound was reopened. The initial anesthesia consisted of a sufficient amount of pentothal and topical cocaine to permit intratracheal intubation. After this the patient was turned on his side and in Trendelenburg position, total spinal anesthesia was induced. This was accomplished with 150 milligrams of novocain and 6 milligrams of pontocaine. On admission to the operating room his blood pressure was recorded as 120/80, the pulse rate was 86. Within 30 seconds of the introduction of the spinal medications, there was a cessation of voluntary respirations. The blood pressure dropped precipitously to a level not recordable and there was no cardiac impulse discernible. Artificial respiration was begun and within 2 minutes a normal respiratory rhythm was resumed. This continued unchanged throughout the entire operation. The scalp, osteoplastic flap, and dura were reflected without any hemostatic instrumentation. The most conspicuous observation, once the cortex was exposed, was the complete lack of cerebral pulsations. There was almost a total absence of discernible blood flow in the cerebral vessels. The alarming venous engorgement visualized at the initial craniotomy exposure was strikingly absent. The picture was reminiscent of the exposed cortex at the time of an unexpected craniotomy mortality but for the lack of any appreciable cortical cyanosis. Throughout the entire procedure, in spite of the lack of cortical pulsation or visible arterial movement, a normal oxygenated appearance of the pial circulation persisted. It was technically a comparatively simple procedure to proceed with ligation of the larger feeding arterial contributors. A total block removal of the lesion and the involved parietal cortex was tremendously expedited, as compared to previous similar craniotomies. There was a surprising minimization of cortical contusion of the adjacent

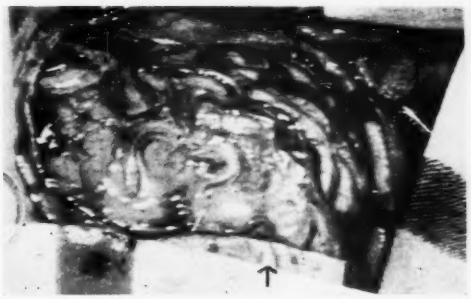


Fig. 2. Initial exposure of the anomaly under conventional anesthesia. The dural reflection is to the longitudinal sinus. Arrow indicates dura.

cortex. There was no cortical staining from subpial hemorrhage. It was possible to accomplish with finesse the delineation of the sensory cortex from the motor convolutions. Technically, great care was initially exercised in controlling the arterial components of the vascular mass, even before ligation of the smallest draining vein. In spite of this precaution, one large venous structure was accidentally ruptured and in contrast to the usual chain of past experiences, there occurred only moderate oozing of blood from this vessel. Ligation after this was easily effected. Under the spinal anesthesia there appeared no actual reduction in the size of the aneurysm as compared to its original craniotomy exposure in Figure 2. The customary alarming and fearsome intertwining vessels were still apparent but compression and even at times purposely rough handling of the lesion did not result in the conventional rupture of these friable blood strutted structures. With the ligation of the venous drainers into

Fig. 3. Surgical pathological specimen. Centimeter scale.

Fig. 4. Postoperative arteriogram made 9 weeks following craniotomy. Silver clip used as a dural marker.

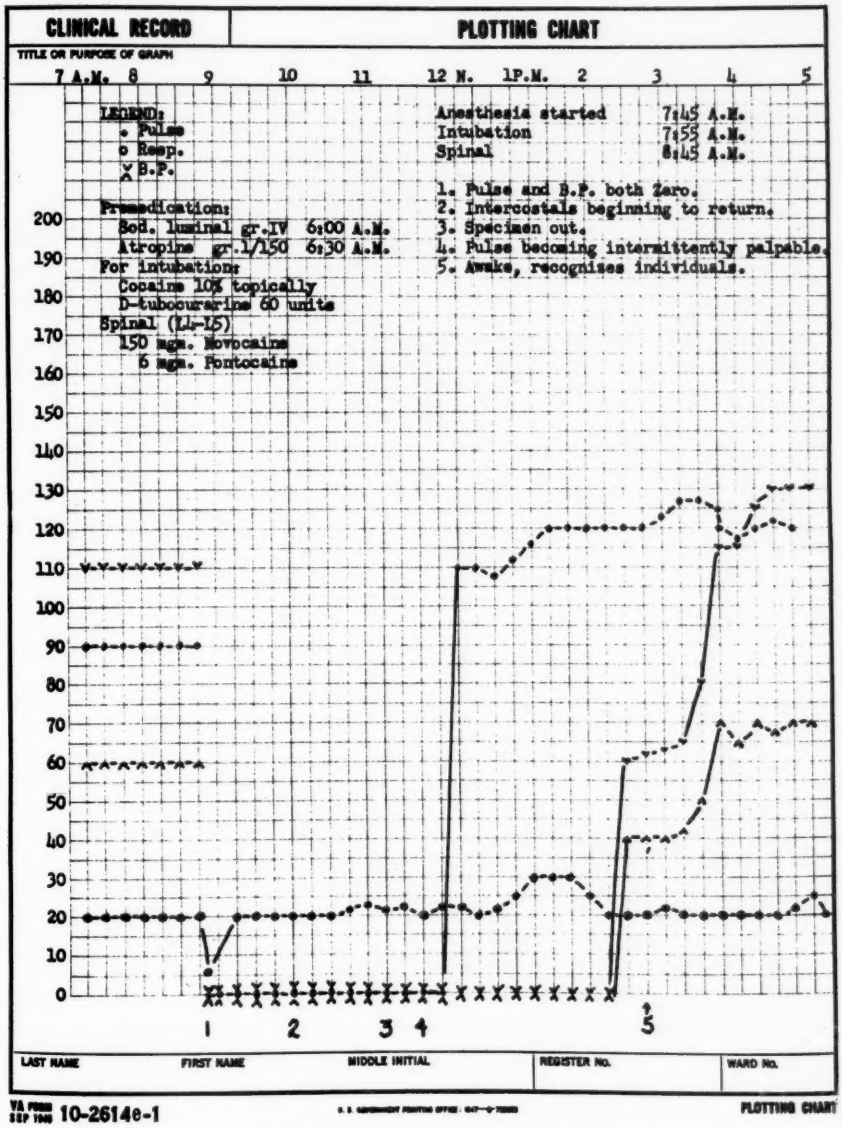
the longitudinal sinus, the entire mass was removed *in toto* (Fig. 3). After this massive extirpation there appeared no bleeding within the medullary cerebral bed. The total operative enucleation consumed no more than 2 hours. This experience was in sharp contrast to the usual many weary hours expended in previous similar surgical undertakings.

After the complete removal of the vascular tumor there appeared feeble cerebral pulsation. In a 30 minute period of further observation, there occurred no cerebral bleeding even though definite arterial bleeding from the dural vessels was seen. Two and one-half hours from the time of the administration of the spinal anesthetic there was a palpable radial pulse. This was counted as occurring 80 times per minute. At this time the blood pressure was not recordable on the sphygmomanometer.

The closure of the dura, skull, and scalp was begun. Neosynephrine and whole blood transfusions were given. There was an estimated loss of approximately 750 cubic centimeters of blood during the procedure and a replacement of 1,000 cubic centimeters of citrated blood was administered slowly. Three hours postspinal medications the patient's blood pressure was discernible and was recorded as 110 systolic and 74 diastolic. One hour after this, the patient began to struggle against the intratracheal tube. Six hours after his intraspinal injection, he was sufficiently alert to respond vocally and to recognize the members of the operating team. His first conversational reaction was that of a prayer which might have indicated somewhat the depths to which he was carried by the spinal anesthesia (Chart 1).

During the 48 hour period immediately following surgery, there was a definite urinary suppression but this complication, somewhat anticipated, was short lived and there were no attending changes in the blood chemistry from the normal. The blood pressure and pulse were stable within some 6 hours of the completion of wound closure. This pressure remained normal during the first 7 postoperative days. The respiratory rate and mechanism were maintained at normal levels without any therapeutic aid. Neurologically, the patient remained alert. There was mental confusion and at times he was irrational, making frequent inquiries regarding his condition. Although a complete left hemiplegia was forecast, a peculiar fluctuating quadriplegia was evident and was not expected. At times there was noted a generalized quadrispasticity which rather promptly gave way to flaccidity. However, on occasions, he was observed spontaneously moving all four extremities. This was initiated on painful stimulation of each member. There was at no time a detectable facial paresis or any aphasia. During his first postoperative week, his mental status remained unchanged. The neurological picture which he presented, we had observed in previous experiences of acquired or traumatic damage to the superior longitudinal sinus (10). Remembering the large number of veins which of necessity had to be ligated in this patient's instance, the explanation for this disturbing postoperative neurological development was evaluated on this venous possibility.

On the seventh postoperative day the patient exhibited a progressive stupor, nuchal rigidity, elevation of the blood pressure and the spastic quadriplegia became constant. At this time focal convulsions of the left side of the face developed. His temperature, which was normal for 3 days before, rose to 104 degrees. There developed an alarming disturbance of the respiratory rhythm. This was not attended by physical or roentgenographic evidences of any pulmonary complications. Spinal puncture on this day revealed xanthochromic but clear fluid under 440 millimeters of water pressure. The cell count on this fluid examination was 130 red blood cells and 32 lymphocytes. The differential diagnosis of an extensive deep venous thrombosis versus a postoperative hematoma was not satisfactorily clinically differentiated. Deciding to err on the side of commission in view of the apparent rapid clinical demise, exploration of the wound was performed. This was done under local anesthesia. There was no evidence of a blood clot nor any active bleeding within the tumor bed. There was, however, an increase in the intrinsic swelling of the adjacent cerebral tissues to a degree that the area of the previous cerebral sacrifice had been almost completely obliterated. The sulci which originally were markedly widened and depressed were now quite flattened. There was a small amount of blood stained fluid in the medullary locus of the


CLINICAL RECORD
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TITLE OR PURPOSE OF GRAPH
7 A.M. 8 9 10 11 12 N. 1P.M. 2 3 4 5
LEGEND:
• Pulse
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Premedication:
Sod. luminal gr.IV 6:00 A.M.
Atropine gr.1/150 6:30 A.M.
For intubation:
Cocaine 10% topically
D-tubocurarine 60 units
Spinal (L1-L5)
150 mgm. Novocaine
6 mgm. Pontocaine
Anesthesia started 7:45 A.M.
Intubation 7:55 A.M.
Spinal 8:45 A.M.
1. Pulse and B.P. both Zero.
2. Intercostals beginning to return.
3. Specimen out.
4. Pulse becoming intermittently palpable.
5. Awake, recognises individuals.
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
1 2 3 4 5
LAST NAME FIRST NAME MIDDLE INITIAL REGISTER NO. WARD NO.
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PLOTTING CHART

Chart 1. Anesthetist's operative chart.

aneurysmal extirpation. There was no gross cortical softening or necrosis of the tumor bed to be seen. The remaining branches of the middle cerebral artery and the main trunk of this vessel appeared quite normal in size and pulsations. The entire adjacent venous network, including the sylvian vein contributors, was demonstrably thrombosed. The wound was closed for the third time. For no explainable reason the patient's condition from this surgery promptly improved.

One week later he still exhibited a fluctuating spastic quadriplegia, mental confusion, and lethargy. He was, however, consistently consciously responsive and his general and neurological course was one of steady improvement. At the end of his second postoperative week, it was possible for the first time to evaluate the sensation responses accurately. There was a bilateral loss of stereognostic sense with some mild impairment of touch sense over the entire left side of the body. He, however, exhibited normal touch localization bilaterally. There was no unilateral or bilateral disturbance in vibratory or position sense and he was cognizant of no divorcement of the left hand, arm, or leg.

Eighteen days after the aneurysmal extirpation the scalp flap evidenced a minor necrosis of its superior rim. An infection of this wound followed with a recession of the scalp flap. A sacrifice of the osteoplastic anemic bone was subsequently necessary. This healing complication was not thought of in the light of a capillary interference due to the total spinal anesthesia but as a result of multiple wound exposures and tissue insults. Two months after the operation the patient exhibited a stable cerebration which he felt was a "clearer mechanism than in the past two years." There has been objective progressive improvement in his motor handicaps. Since this same convalescent recovery has been previously duplicated in a previous instance of a total removal of an extensive occipital lobe arteriovenous aneurysm performed under conventional anesthesia, the motor residuals were not attributed to the effects of the spinal anesthesia.

The technique of total spinal anesthesia is not a new procedure. Likewise, the utilization of this method of anesthesia in the surgical management of lesions of the head and neck has not only been helpful as reported by Morton and Jonnesco but apparently is a safe undertaking. Vehrs has shown both experimentally and clinically that the extent to which the motor and sensory cranial nerves and the medullary centers were affected, depended upon the concentration and volume of novocain used. In order to prevent fatal cerebral ischemia and to assist the venous return to the heart, he insisted that the Trendelenburg position be maintained. In a series of 84 operations for thoracolumbar splanchnicectomy and sympathectomy, Griffith and Gillies have reported no instances of permanent dysfunction of the central nervous system; this, in spite of the fact that 4 of their patients had histories of previous serious cerebral insults.

It is proposed that, in the future use of this method of anesthesia, supplemental anesthesia of other types will be disposed of and that the dose administered intraspinally to the patient in this case will be materially reduced. Perhaps fractional dosages of spinal anesthesia might prove more effective for its technical contribution in the extirpation of these particular cerebral vascular congenital anomalies.

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POSTEMETIC RUPTURE OF THE ESOPHAGUS

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POSTEMETIC rupture of the esophagus is an intrathoracic catastrophe which is universally fatal if untreated. It should be the subject of continued scrutiny. The tragedy probably strikes more often than is generally suspected. Four cases are known to have occurred in the metropolitan Oakland area within a 6 months' period. Two were only recognized terminally; 2 were correctly diagnosed within a few hours and are the subject of this report.

CASE REPORTS

CASE 1. Mr. T. D., aged 55 years, was in good health until the evening of December 18, 1948, when he attended a banquet and ate and drank considerably. He retired at midnight and there were several episodes of vomiting shortly thereafter. At 3:00 a.m. a severe vomiting attack was followed by epigastric pain but the details were vague in the patient's mind. Indigestion continued and was unrelieved by soda and enemas. Because of increasing distress, Dr. Gordon Roberts made a house call at 11:00 a.m. The patient was apprehensive and slightly dyspneic. There was localized pain over the lower sternum and upper abdomen with exquisite epigastric tenderness. Emergency hospitalization was recommended. On the basis of history, fulminating course, and physical findings the correct diagnosis was suggested over the telephone by Dr. Dan Tucker, radiologist at Peralta Hospital. Roentgenograms were confirmatory of rupture of the esophagus (Figs. 1, 2, 3). While being examined roentgenologically there was rapid deterioration. The patient became cyanotic and maniacally restless. The excruciating substernal and epigastric pain was unrelieved by opiates. The blood pressure fell to 80/40, the pulse rate rose to 140 beats per minute, and respirations became 36. The voice developed a nasal twang and this was *followed* by the appearance of subcutaneous emphysema in the neck.

The patient was transferred directly to the operating room from the x-ray department. Oxygen was given and 600 cubic centimeters of plasma rapidly administered while the blood was being crossmatched. By 4:00 p.m. the pressure was stabilized at 110 (although the pulse rate remained from 140 to 150). Blood was started and endotracheal anesthesia was induced. From the anesthesiologist's viewpoint, the risk was classified as desperate. The operation was commenced shortly thereafter, approximately 13 hours following the rupture (P.C.S. and David J. Dugan). The pleural cavity was rapidly entered through the bed of the resected ninth rib posteriorly. Nearly 1,000 cubic centimeters of turbid, amber fluid without odor was present. The tissue reaction was intense; the pericardial fat was fiery red. The lower mediastinum was bulging, edematous, and blackened although there was no gross perforation. The mediastinal pleura was widely opened with the escape of odorless air and thin discolored fluid. It was notable that with the release of pleural and mediastinal pressures, the blood pressure rapidly stabilized at 130, the pulse at 120, and the patient's condition remained relatively good throughout the operation which consumed 2½ hours. Fifteen hundred cubic centimeters of blood were given.

The exposed esophagus was carefully inspected. Just above the diaphragm there was a longitudinal rent, 1 centimeter in length, through which stomach contents were regurgitating. *Except for acute periesophageal inflammation, the esophageal tissues were normal and there was no chronic ulceration or esophagitis.* A Levin tube was passed into the stomach from above and the defect was closed in layers with No. 0000 silk. The mediastinum was extensively débrided by curettage, the removal of strips of grossly necrotic tissue and repeated laving with saline solution. Two right-angle drainage tubes were placed in the pleura to be connected with water-seal bottles. No attempt was made to close the mediastinum; it was left wide open and drained into the pleural cavity. Penicillin was administered by the intravenous and intramuscular routes during surgery and 200,000 units were placed in the pleural cavity after the chest was closed. Immediate postoperative bronchoscopy was necessary because of retained secretions.

The benignity of the postoperative course was amazing. The lung expanded almost immediately and the impending empyema was thereby aborted. The posterior intercostal tube drained a small amount of thin purulent material for 4 days and was then removed. The Levin tube was withdrawn on the fifth day and clear fluids started by mouth. The patient was discharged from the hospital on the fifteenth day following operation on a full diet and with a solid uninfected wound. He has remained well. Follow-up barium studies 2 months after discharge showed the esophagus and stomach to be normal.

CASE 2. Mr. E. K., aged 45 years, was admitted to Providence Hospital, Oakland on June 2, 1949, at 4:00 p.m. For the 2 previous days there had been moderate overindulgence in alcohol with some

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Fig. 1. Flat plate of abdomen. This is the correct angle of exposure since it covers the region above the diaphragms. No subdiaphragmatic air is seen but there is loculated air obviously trapped in the mediastinum behind the heart.

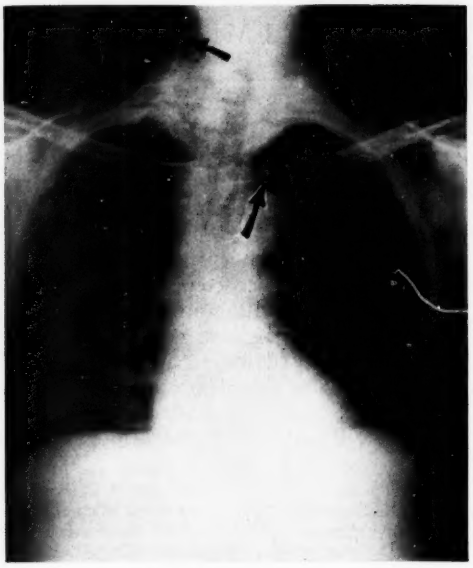


Fig. 2. Frontal projection of chest. A small amount of air has dissected up the mediastinum. It is overlying the aortic knob and is in the fascial planes of the neck. *No* free fluid can be detected in the left pleural cavity although at operation 3 hours later 1,000 cubic centimeters of fluid were removed.

vomiting. Three hours before admission the patient vomited gastric contents and about a half a cup of blood. This was followed by epigastric and lower thoracic pain on the left. The pain became rapidly more severe and radiated somewhat to the back. Dr. Philip Matzinger saw the patient 2 hours after his acute episode. Morphine was given and the patient was sent at once to the x-ray department. On arrival he was dyspneic and cyanotic. The voice had a nasal tone and there was slight crepitus in the left side of the neck anteriorly. The heart was rapid and regular, the thready pulse averaging 130 beats per minute. The blood pressure was 140/70. The lungs showed scattered crepitant râles especially on the left. There was flatness on percussion and absent breath sounds in the lower half of the left chest posteriorly. The abdomen showed considerable tenseness of the muscles in the epigastrium on both sides but there was no board-like rigidity nor tenderness. Peristaltic sounds were present but feeble. The white cell count was 18,000. The suspected diagnosis of esophageal rupture was confirmed radiologically by 5:00 p.m. (Figs. 4 a and b).

There then ensued a seemingly insurmountable delay in getting the patient to the operating room and appreciable deterioration in his condition was noted. Oxygen was given and plasma was started pending a cross-match with whole blood. At the time of anesthetic induction the blood was running. The patient was cyanotic, restless, and was rated as a very poor risk even though the blood pressure was maintained at 140/90.

The operation was commenced approximately 8 hours after the rupture and lasted 2½ hours (P.C.S. and D. J. Dugan). At the end of operation the patient's condition was infinitely better than at the start. The pleural cavity was rapidly entered posteriorly by a 20 centimeter incision through the eighth intercostal space. Two thousand cubic centimeters of murky, nonodorless fluid was evacuated. Gram stain and culture showed anaerobic streptococci, both viridans and hemolyticus. The pleura was intensely congested. The mediastinum was swollen. Air and fluid poured through a small perforation in the mediastinal pleura which was rapidly incised from the arch to the diaphragm. Partial mobilization of the esophagus revealed a 3 centimeter longitudinal rent lying posterolaterally. The dilated stomach was decompressed through this rent. As with the first case, this patient's condition improved remarkably as soon as the pleural and mediastinal pressures were reduced. The rent extended into the hiatus so that partial dissection of the diaphragmatic muscle was necessary to visualize

the inferior margin of the tear. The wall of the esophagus showed a severe acute inflammatory reaction but the mucosa was normal. There was no evidence of ulcer, esophagitis, or other pre-existing disease.

A stomach tube was passed from above and the defect repaired in layers with interrupted No. 0000 silk. An external buttress was fashioned from remnants of mediastinal areolar tissue and pleura. The mediastinum was débrided extensively from diaphragm to arch by combined sharp and blunt excision of grossly diseased tissue (Fig. 5). Generous lavage was carried out and the mediastinum left wide open. A right-angled tube was placed in the seventh interspace in the midaxillary line, and the lung re-expanded satisfactorily. The thoracic wall was closed with interrupted fine silk. Penicillin was administered intravenously, intramuscularly, and intrapleurally.

Patchy bilateral atelectasis occurred in the immediate postoperative period because the patient would not cough. There was also a severe penicillin reaction. Good peristalsis was heard by the third postoperative day and the Levin tube was removed. The patient was discharged on the thirteenth postoperative day. The wound was solid and he was on a full diet. Six weeks after operation, barium studies of the esophagus were normal.

Fig. 3. Esophagogram using lipiodol. The loss of continuity in the lower esophagus is obvious. In any case of suspected perforation or rupture, lipiodol is far preferable to barium. Once the latter has infiltrated the mediastinal areolar tissues it is very difficult to remove.

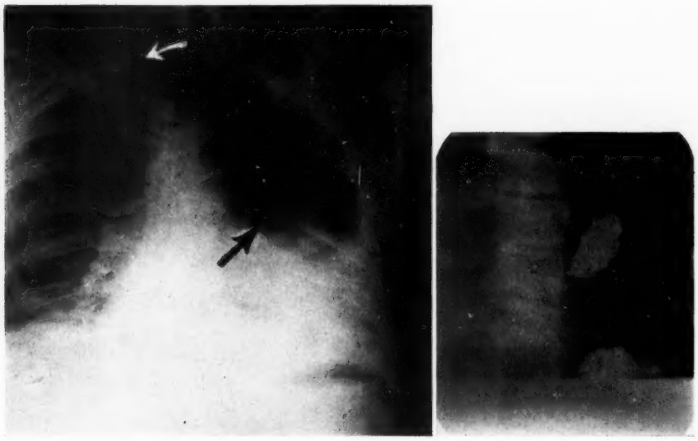
DISCUSSION

No useful purpose is served by an extensive summary at this time. Suffice it to say that the literature goes back to Boerhaave's classic description of the death of the Grand Admiral of Holland in 1724. Those interested in detailed reviews are referred to the reports of Fitz, Walker, Klein and Grossman, Eliason and Welty, Barrett (5), and Kinsella and associates.

This killer is often labeled "spontaneous perforation" of the esophagus. I submit that in the majority of instances this is a misnomer. Apparently spontaneous perforations *have* occurred at the site of an ulcer (24, 29) or following neurosurgical operations (14, 16). In most reported instances, however, vomiting (frequently following alcoholic overindulgence) is prominent in the history. The initial and frequently agonizing pain of the perforation is intimately associated with, or immediately follows one of the spasms of regurgitation. When there is no pre-existing esophageal disease the term "rupture," implying the application of force, is more appropriate and the lesion should be considered of traumatic rather than of spontaneous origin. It is of considerable interest that at least one large insurance company acknowledges this interpretation and has reimbursed a patient on the basis of an accidental or traumatic causation for his esophageal rupture rather than on the basis of disease (Case 2).

Experimentally, the esophagus will rupture (and almost always does so just above the diaphragm) if sufficient pressure is applied from within (27). Such pressures must be frequently exceeded during the act of vomiting. Whatever the protective mechanisms, at rare times one of several untoward events takes place. Complete lack of muscular coordination may develop during vomiting with resulting unduly high intraesophageal pressures; there may ensue the temporary impaction of a regurgitated bolus of food in the lower esophagus with increasingly forceful retching during the attempts to dislodge the obstruction.

Lerche has described the structural details of the esophagus and the complicated mechanics of the gastroesophageal segment. He



a b

Fig. 4. a, Frontal projection of the chest. There is air in the mediastinum and in the neck. Free fluid is present in the left pleural cavity. b, The swallowed lipiodol has infiltrated the tissues of the lower mediastinum just *above* the diaphragm.

believes the spiral distribution of the inner muscular coat in the lower esophagus is implicated. The following train of circumstances may be responsible for rupture during attempted regurgitation: spasm of the spiral constriction closing the upper end of the lower esophageal segment; inferiorly, the segment is closed by the constrictor cardiae, gastroesophageal vestibule, and inferior esophageal sphincter all in a state of contraction. In an attempt to propel the contents against the upper obstruction there is caused a bulging of the esophageal wall between the bands of the spiral musculature. With increasing pressures, the contraction of these spiral fibers may suddenly be released (the "critical point" of Ganter) and rupture of the wall may then take place.

If trauma can be argued then it would seem to make little difference whether the force is applied by an operator (such as perforation during esophagoscopy), whether it comes from an external source (such as tearing from a missile), or whether the force was actually engendered by the patient himself with the probable creation of unduly high intraesophageal pressures during vomiting.

My primary interest here has to do with treatment. There recur in the literature references to "mediastinotomy and drainage" and "pleural cavity drainage." "We question the wisdom of immediate repair in patients whose desperate condition is a strong contraindication to any major surgical procedure" (33). "After a diagnosis some benefit might be obtained by surgical drainage of the territory as emergency surgery without transfer to the operating theatre . . . definite plastic repair . . . as a later elective procedure" (16). "Surgical repair of the esophagus . . . a truly formidable procedure to perform on a desperately ill patient" (19). "Almost all patients with rupture of the esophagus should be treated medically and rarely surgically" (38).

Such reasoning is wholly illogical and ignores the basic pathology. The lesion in question has resulted from rupture of a normal or relatively normal hollow viscus. Experiences during the recent war emphasized repeatedly the fatal fallacy of watchful waiting or drainage in treating wounds of hollow viscera. Prompt resuscitation, exploratory operation, and closure of the rents were the guiding precepts. It ill behooves either thoracic or general surgeon to ignore these tenets just because the hollow viscus happens to be in the chest. Of course, these patients are

sick unto death but the fatal outcome cannot be escaped unless the rent is closed. So-called "conservative" drainage procedures have no place in the early hours after rupture.

In the rare patient who does weather the initial insult of a fulminating mediastinopleuritis and survives for more than 24 hours, invasive infection must presumably be established in the esophageal wall, mediastinum, and pleura, and a direct attack upon the esophagus may well fail at that time. Temporizing drainage procedures combined with an enterostomy for feeding purposes may then succeed but the convalescence is greatly prolonged and multiple operations are the rule (Table II).

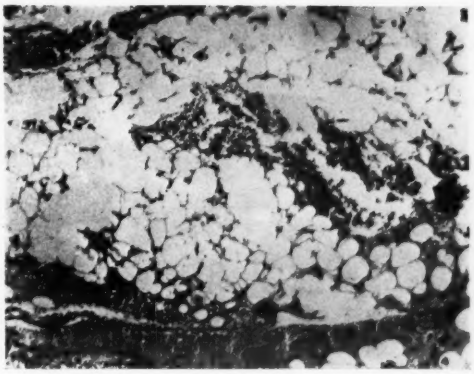


Fig. 5. Photomicrograph shows the extent of the fulminating mediastinal contamination which has developed within 8 hours. There are massive acute fibrinous inflammation, *early* neutrophilic invasion, and patchy fat necrosis. ×465.

COMMENTS ON TABLES I AND II

All reported cases which were subjected to surgery have been summarized in Tables I and II. The order of listing in both tables is on the basis of the length of time between rupture and operation. The 15 patients listed in Table I were all subjected to definitive exploration and repair of the esophageal lesion. All were thoracotomies except Foggitt who performed a laparotomy, dissected the esophagus free, and pulled it down into the abdomen for suture. Abbott performed a resection of the lower esophagus with esophagogastric anastomosis.

Five patients died following these operations and 10 lived, a mortality rate of 33⅓ per cent. Of the 10 living patients, 5 had an extremely rapid convalescence without complications (13 to 22 days). It is of interest that all these operations were performed within 15 hours after the rupture. The other 5 patients had a prolonged convalescence. Of the 5 patients operated upon 20 or more hours after rupture 1 died and the convalescence of the remaining 4 was prolonged.

For the record, certain factual data should be tabulated. Apparently the first thoracotomy was that of Collis in 1943. Unfortunately, the patient died. Apparently neither blood nor antibiotics were given. The first successful thoracotomy and repair was performed by Barrett (4) in 1946.

In Table II are listed all patients on whom some type of drainage procedure was performed as contrasted with thoracotomy and definitive repair of the esophagus. Seven of the 15 patients died and 8 lived, a mortality rate of 47 per cent. In all who survived, convalescence was greatly prolonged (6 weeks to 1½ years). Five of the 6 patients operated upon within the first 24 hours died promptly. Thus it can be seen that during the stage of contamination, drainage procedures are essentially useless. For those who happened to survive without surgery until infection was established, drainage procedures were of considerable value.

DIAGNOSIS

Postemetic rupture of the esophagus must be differentiated from perforated peptic ulcer, acute pancreatitis, empyema of the gall bladder, acute coronary occlusion, and spontaneous pneumothorax. *If the lesion is kept in mind*, the symptoms become practically pathognomic and on more than one occasion the correct diagnosis has been suggested over the telephone by a perspicacious consultant. Differentiation from perforated peptic ulcer should be particularly emphasized since in a number of cases which have been reported patients have been subjected to exploratory celiotomy (5, 15, 32). Of course in this unhappy event, no abdominal pathology has been found.

TABLE I.—RUPTURE OF THE ESOPHAGUS—THORACOTOMY

Surgeon	Hours from rupture		Postoperative complications	Secondary operations	Outcome
	to diagnosis	to operation			
1. Clagett (34)	2	3	Superficial wound infection	none	Cured, 21 days
2. Kinsella, Case 5 (27)	5	8	Pulmonary embolus, 9th day	none	Died, 9 days
3. Samson, Case 2	5	8	Patchy atelectasis severe penicillin reaction	none	Cured, 13 days
4. Collis (12)	6	9	Shock	none	Died, 21 hours postop.
5. Barrett, Case 3 (3)	6	9	Esophageal fistula, empyema	none	Cured, several weeks
6. Cliffton, Case 1 (11)	5	9	D.t.'s, thrombophlebitis	none	Cured, 22 days
7. Barrett, Case 2 (4)	6	10	Esophageal fistula, mediastinal abscess, pulmonary abscess	Drainage of abscess, enterostomy	Cured, 11 weeks
8. Lynch, Case 3 (31)	10	12	none	none	Cured, 14 days
9. Cliffton, Case 2 (10)	8	12	Esophageal fistula, bilateral empyema	Drainage of empyema	Died, 11 weeks
10. Samson, Case 1	10	13	none	none	Cured, 15 days
11. Foggitt (18)	16	20	Mediastinal abscess	none	Died, 48 hours
12. Scholefield (35)	16	20	Esophageal fistula, empyema, wound infection	none	Cured, 13 weeks
13. Allison (2)	17	22	Esophageal fistula, empyema	Esophageal repair, jejunostomy, drainage of empyema	Cured, 6 months
14. Lynch, Case 2 (31)	10	30	Esophageal fistula, empyema	Drainage of empyema, jejunostomy	Cured, 6 weeks
15. Abbott (1)	24	48	Esophageal fistula, empyema	Drainage of empyema, jejunostomy	Died, 9 months

Frequently, the patient has been overfree in his use of alcohol. There ensues vomiting of blood-streaked material, severe substernal and epigastric pain, and great physical deterioration within a few hours. On examination, one is impressed by the severe pain, restlessness, and board-like rigidity of the abdomen. One's attention is directed to the chest by dyspnea, cyanosis, and crepitus in the neck. A nasal twang to the voice is frequently present and may be of extreme importance since it often precedes the appearance of neck crepitation by several hours.

Whether or not the diagnosis is suspected at this point, it will be at once apparent to the examiner that the patient belongs in the hospital. He should be admitted directly to the x-ray department. It is of value to have the laboratory technician standing by so that an immediate blood typing and crossmatch can be performed. A flat plate of the abdomen is frequently ordered first to rule out a perforated peptic ulcer. Tucker stresses the necessity of uniformly taking this view high enough to study the diaphragms and lower mediastinum. Presence of loculated air overlying the heart shadow will practically clinch the diagnosis. Further chest films may or may not demonstrate pleural fluid but will always show air in the mediastinum. A swallow of lipiodol (never barium) will localize the tear.

Sooner or later, the patient develops a shock-like state which is due to a combination of: (1) contamination, (2) pain, (3) anoxia. Speed in the preoperative resuscitation is of paramount importance and *the preliminary steps should be taken in the x-ray department.* A Levin tube with continuous suction should be inserted under the fluoroscope to be certain that the tip lies in the stomach. Some (12, 19) have questioned the necessity of a stomach tube since the patients do not vomit following rupture. It is our experience, however, that there is a continuous back flow through the rupture from a dilated

TABLE II.—RUPTURE OF THE ESOPHAGUS—DRAINAGE PROCEDURES

Surgeon	Hours from rupture		Type of operation	Postoperative complications	Secondary operations	Results
	to diagnosis	to operation				
1. Gardner (21)	7	7	Drainage posterior mediastinum	Esophageal fistula, mediastinal abscess	none	Cured, 6 weeks
2. Kernan (26)	7	9	Drainage superior mediastinum	Mediastinitis	none	Died, 17 hours
3. Kinsella, Case 3 (27)	5	10	Intercostal drainage pleura	Shock, empyema	none	Died, 3 days
4. Strieder (40)	12	14	Intercostal drainage pleura	Bilateral empyema	Drainage posterior mediastinum	Died, 42 hours
5. Cleland (9)	20	22	Intercostal drainage, pleura	Shock, empyema	none	Died, 24 hours
6. Clagett (25)	20	24	Exploration mediastinum and drainage	Bilateral empyema, mediastinitis	none	Died, 40 hours
7. Lynch, Case 1 (31)	50	60	Intercostal drainage, pleura	Esophageal fistula, empyema	Drainage empyema, close fistula ×4, jejunostomy	Cured, 1½ years
8. Barrett, Case 1 (5)	Autopsy	6 days	Intercostal drainage, pleura	Esophageal fistula, empyema	none	Died, 9 days
9. Frink (19)	26 days	7 days	Intercostal drainage, pleura	Esophageal fistula, empyema	Thoracotomy and pack	Cured, 4 months
10. Overholt (13)	8 days	8 days	Rib resection, bilateral empyema	Esophageal fistula, empyema	none	Cured, 11 weeks
11. Moore (33)	14 days	14 days	Rib resection, empyema	Esophageal fistula, empyema	Jejunostomy, esophagogastroplasty	Cured, 6 months
12. Vestal (37)	24 hours	14 days	Drainage empyema	Esophageal fistula, empyema	none	Cured, 2 months
13. Kinsella, Case 4 (27)	17 days	17 days	Intercostal drainage, pleura	Total empyema	none	Died, 26 days
14. Graham, Case 1 (22, 23)	Followed drainage of empyema		Rib resection, empyema	Esophageal fistula	none	Well after many months
15. Graham, Case 2 (22, 23)	Followed drainage of empyema		Rib resection, empyema	Esophageal fistula	none	Well after many months

stomach. Therefore, a stomach tube must be inserted. Oxygen should be supplied by a nasal catheter or mask. Intravenous plasma should be commenced while waiting for typing and cross-matching of blood.

Ideally, the patient should be transported directly from the x-ray department to the operating room for continuation of resuscitation. Too much time usually is wasted in x-ray and on the ward before taking the patient to surgery. Every lost hour greatly decreases the chances of rapid recovery without complications. As Beecher (6, 7) has indicated, resuscitation can be accomplished within 3 hours. It is well to remember that surgery is an integral part of resuscitation and must be carried out as soon as the patient is in shape. Beecher has stressed that adequate response to resuscitation consists of a systolic blood pressure of from 80 to 85 in a patient of good color and with a warm skin. If, however, the shock state persists even though the blood pressure is within normal range surgery must be undertaken. It is a losing battle to attempt to correct overwhelming and continuing contamination without surgery.

In the operating room and prior to surgical exploration frequent chest examinations are necessary. Even though no pleural fluid may have been discernible on the roentgen plate it may collect with amazing rapidity and as much as 1,000 cubic centimeters or more may become noticeable in an hour or so. Such

an amount should be aspirated to give the patient all the breathing space possible.

Blood should be started as soon as available. The first 500 cubic centimeters should be given within 20 to 30 minutes, and the second 500 cubic centimeters slowed down depending on the time that surgery is to be commenced.

Antibiotics should be used early and freely. Since the infection is mixed, one should not depend entirely on a single antibiotic. Five hundred thousand units of crystalline penicillin and 500 milligrams of aureomycin should be given in the first intravenous medication. Depot penicillin should be given at the same time and continued following operation as should intravenous aureomycin. Study of gram stains and cultures from the pleural and mediastinal fluid may later cause some change in the antibiotic therapy.

ESSENTIALS OF SURGERY

These are exemplified in the 2 cases described previously. Direct exposure at thoracotomy as soon as possible is the *sine qua non* for a successful outcome. The "critical period" seems to be approximately 15 hours. Prior to that time the tissues are in a state of contamination but invasive infection apparently has not yet developed. The repair should be layered whenever possible using preferably fine nonabsorbable suture material. This will hold in contaminated tissue but will not necessarily hold in infected tissues.

Thorough débridement of the mediastinum is essential. This means not only opening of the mediastinum but rapid dissection and curettage as far as the discoloration extends. Occasionally, the need for opening the mediastinum above the arch of the aorta is obvious. When this stage of the operation is reached one may relax a bit since there is universal observation of rapid appreciable improvement in the patient's condition as soon as the mediastinum has been opened (4, 31, 34). Following débridement, there should be generous lavage of the open mediastinum and the pleural cavity with several quarts of warm saline solution. We favor the use of one and even two intercostal tubes in order to re-expand the lung as rapidly as possible.

SUMMARY AND CONCLUSIONS

Postemetic rupture of the esophagus is not spontaneous in the accepted sense of the word but is traumatic in origin.

Rupture of the esophagus is rare but is not a pathological curiosity. The signs and symptoms are practically pathognomic and a suspected diagnosis can be confirmed with ease if the lesion is kept in mind.

It is uniformly fatal if undiagnosed and untreated.

The essentials of treatment consist of rapid resuscitation, and thoracotomy with definitive repair of the esophageal rupture. So-called "conservative" drainage procedures have no place in the early hours following rupture.

If, by rare chance, the patient survives the initial contamination for from 24 to 48 hours, invasive infection may be presumed present and temporizing drainage procedures may then be indicated.

Two cases of rupture of the esophagus are added to the literature. In each, the diagnosis was made early, resuscitation was intensive, and prompt recovery followed thoracotomy and direct repair of the esophageal tear.

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RADIOIODINE UPTAKE BY THE FETAL MOUSE THYROID AND RESULTANT EFFECTS IN LATER LIFE

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THE use of radioactive iodine during pregnancy has been greatly restricted because of the uncertainty of the effect of therapeutic doses on the fetus (26). This isotope occupies an established place in the treatment of certain diseases of the thyroid, particularly hyperthyroidism and carcinoma. Iodine ingested by the mother passes readily through the placenta and into the fetus. The thyroid gland begins to function during fetal life. There are several types of evidence of the gland's activity *in utero*. Colloid makes its appearance in the developing follicles. A progressive increase occurs in the concentration of iodine and iodine-containing compounds. Extracts, implants, or feedings of the fetal gland are capable of inducing metamorphosis in amphibian larvae. Finally, recent experiments with radioactive iodine have shown significant uptake of I^{131} by the fetus following the administration of tracer doses to the mother during pregnancy.

This report presents experimental observations concerning the uptake of iodine by the thyroid gland of the fetal mouse and the late effects of a transplacental dose of the radioactive isotope on the structure of the thyroid and pituitary glands and the development of the offspring. The observations to be reported concern the stage of development at which the fetal gland assumes the capacity to concentrate iodine, the increase in iodine-concentrating power with fetal age, a correlation of this function with histologic structure, the pathologic changes induced in the fetal as compared with the maternal thyroid by therapeutic doses of I^{131}, and the effect of intrauterine irradiation of the gland upon subsequent growth and function in the offspring. Despite the differences between mouse and man, certain basic facts which have emerged from this study may be applicable to clinical problems in the human.

White mice of an inbred Swiss strain which had been maintained on a low iodine diet were injected subcutaneously with a single dose of approximately 200 microcuries of carrier-free I^{131} (8 day half-life) in groups at various stages of dated pregnancies. Forty-eight hours after injection representative animals from each group were killed and the maternal thyroids were serially sectioned. The fetuses were removed promptly and the entire body radioactivity of several was measured, either directly or following hydrolysis in sodium hydroxide. Serial histologic sections were prepared of the thyroids of the remaining fetuses. The rest of the pregnant animals in each group were allowed to deliver normally at term, about 20 days in this strain of mice. The offspring remained with their mothers until weaned at 22 days and were weighed twice weekly for periods up to 1 year. Representative young were autopsied at various ages. Parallel observations were made on control animals for each group.

UPTAKE OF RADIOIODINE BY THE FETAL THYROID

Partition of fetal iodine. Retention of iodine within the fetus provides presumptive evidence of thyroidal activity, but this requires proof by direct experiment. A separate group of 6 mice were injected on the eighteenth day of pregnancy with a single dose of radioiodine (174 to 190 microcuries) for comparison of total body versus thyroid radioactivity. The animals were killed 7 hours, 18½ hours, and 48 hours later, respectively. Measurements were then made of the radioactivity of several of the individual fetuses, following which similar measurements were made on the extirpated thyroid glands, which were removed intact

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and still attached to the trachea. The results are tabulated in Table I. At 7 hours each fetus contained an average of 3.2 per cent of the iodine given to the mother. By 18½ hours most of this had been lost by excretion and only an average of about 1 per cent of the maternal dose remained in each fetus. No significant change occurred from this point until 48 hours, when an average of about 1 per cent of the original activity was still present in each fetus. All measurements of radioactivity were corrected for decay.

Coincident with the decrease in total fetal iodine during the 48 hours following injection of the mother with I^{131}, the iodine content of the thyroid gland likewise diminished, but at a considerably slower rate. At 7 hours an average of 0.32 per cent of the initial amount of maternal I^{131} was present in each fetal thyroid. By 18½ hours the concentration had dropped to only 0.22 per cent, with no significant change (0.24 per cent) by 48 hours. This reflects the great affinity of iodine for the thyroid gland, in comparison with the blood and other tissues of the body, from which the initial high concentration of iodine was rapidly lost. As a result the percentage of total fetal I^{131} which was in the thyroid increased progressively during the 48 hours following injection of the mother. At 7 hours an average of 10.4 per cent of the total fetal I^{131} was present in the thyroid. This percentage increased to an average of 24.7 per cent at 48 hours. Under the conditions of these experiments, therefore, approximately one-fourth of the I^{131} present in the fetus 48 hours after injection of the mother was concentrated in the fetal thyroid. This is a much smaller fraction of the total body I^{131} than exists in the adult thyroid after 48 hours, by which time after injection most of the nonthyroidal I^{131} has been excreted. A possible source of extrathyroidal I^{131} in the fetus is circulating radioactive thyroxine transmitted from the mother.

Onset of thyroid function. Iodine is present in the normal thyroid gland in about 25 times its concentration in the serum (28). Since concentration of this element by the thyroid is one of its specific and unique functions, the localization of radioiodine in the gland serves as an excellent quantitative indicator of its functional capacity. Experiments were performed at various stages of pregnancy, beginning with the 13th day. Table II shows the radioiodine content of the fetuses 48 hours after injection of the mothers. The fetuses of mothers injected on the 13th, 14th, and 15th days showed no measurable uptake of I^{131}, the averages shown for these days in the table representing little more than background measurements of radioactivity. Small but significant concentrations of iodine were found in the fetuses of mothers injected on the 16th day. This therefore represents the earliest stage of specific thyroidal activity in the fetal mouse. The gland's capacity to concentrate iodine increased rapidly from this stage until the end of pregnancy (Fig. 1). This increase far exceeds the rate of growth of the gland or of the fetus as a whole during the same period, as can be seen by comparison of the body growth curve with the curve of I^{131} uptake. It has been shown by Hall and Kaan that in the rat little growth of the thyroid occurs in the last 4 days of intrauterine life, the rate of

TABLE I.—RATE OF UPTAKE OF IODINE BY FETUS AND ITS PARTITION IN FETAL THYROID*

	7 hours	18½ hours	48 hours
Average per cent of maternal dose in fetus (6 animals)	3.2 (2.7–4.1)	0.99 (0.64–1.36)	0.97 (0.77–1.31)
Average per cent of maternal dose in fetal thyroid (7 animals)	0.32 (0.20–0.40)	0.22 (0.11–0.33)	0.24 (0.17–0.31)
Average per cent of fetal I^{131} uptake in thyroid (7 animals)	10.4 (6.2–14.3)	22.0 (18.1–26.1)	24.7 (18.7–34.8)

*Animals injected on 18th day of pregnancy with 174–190 microcuries of I^{131}.

TABLE II.—IODINE UPTAKE BY FETUS IN RELATION TO STAGE OF DEVELOPMENT

Day of pregnancy	No. of mothers	No. of fetuses	I^{131} uptake by fetus (percentage of maternal dose)	
			Range	Average
13	7	73	0.0011–0.0044	0.0023
14	7	78	0.0034–0.0124	0.0063
15	6	64	0.0063–0.0220	0.0125
16	10	91	0.0150–0.138	0.0388
17	8	73	0.061 –0.226	0.125
18	7	54	0.257 –0.842	0.504
19	6	55	1.6 –3.6	2.77

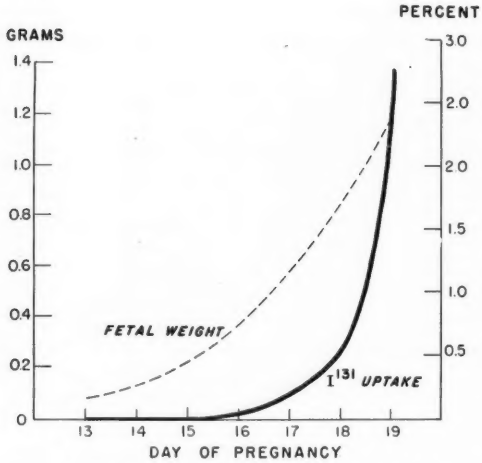

Fig. 1. Uptake of iodine by fetal mouse in relation to stage of development. Iodine uptake is expressed as per cent of maternal dose of I^{131} in fetus 48 hours after injection at indicated stage of pregnancy.

growth of this organ lagging behind that of the fetus as a whole.

Evidence of iodine uptake was obtained by Gorbman and Evans (15) in radioautographs of the fetal rat thyroid 48 hours after injection of the mothers at 18 to 19 days of gestation, but not earlier. Since gestation in the rat is only about 21 days, this means that iodine storage in the fetal thyroid does not begin until 2 to 3 days before term. In the human fetus, on the other hand, radioactivity has been demonstrated in the thyroid gland after administration of a tracer dose of I^{131} to the mother as early as the 14th week of gestation (3).

TABLE III.—AGE OF FETUS AT ONSET OF IODINE STORAGE*

	Rat	Pig	Sheep	Bovine	Human
Gestation time (days)	21	120	150	285	265
Author					
Fenger (1912)				3 months	
Fenger (1912)			3-4 months		
Fenger (1912)		70 days			
Hogben and Crew (1923)			3 months	4 months	
Maurer (1927)					7 months
Nosaka (1927)					6 months
Lelkes (1933)					4 months
Rankin (1941)		46-50 days			
Gorbman and Evans (1943)	18-19 days				
Chapman and others (1948)					14 weeks
Wolff and others (1949)				60 days	

*Partial summary of literature

Chemical determinations of fetal thyroidal iodine in various species have revealed selective storage of the element at different stages of intrauterine development (Table III). This iodine exists in organically-bound, thyroxine-like form, as well as in the water-soluble inorganic form (21, 29).

Confirmatory evidence of the functional status of the fetal thyroid has been obtained by bioassay of the gland itself. Extracts prepared from the thyroids of 9 centimeter (crown-rump length) pig fetuses (but not 7 cm. fetuses) stimulated metamorphosis in hypophysectomized tadpoles, in a manner comparable to the action of adult thyroids (32). Similar results were obtained with extracts of rat fetal thyroids after the 17th day of pregnancy (18) and with bits of human fetal thyroids from the third month of gestation (33). Precipitin reactions have established the presence of thyroglobulin in the human fetus in the third and fourth months (19).

Correlation of thyroid histology and iodine uptake. Previous investigations on the rat (15, 18), pig (22, 32), bovine (21), and human (3) have indicated a nice temporal relation between the appearance of colloid-containing follicles in the fetal thyroid and the content of iodine in the gland. The present study confirms this relation in the mouse. Follicles began to appear in the fetal thyroid for the first time between the 16th and 17th days, the stage at which collection of radioiodine began (Fig. 2). Colloid storage, first detectable in the 17 day fetus, increased progressively to term, synchronously with the rising iodine concentration of the thyroid.

PATHOLOGICAL EFFECTS OF RADIOIODINE

An adult mouse, which weighs about 30 grams, has a thyroid of about 4 milligrams. The maximum thickness of the gland is 1.2

millimeters and in most places it is less than 1 millimeter wide or thick (31). Radioiodine deposited in it emits both beta and gamma rays. The gamma rays are highly penetrating; they therefore escape from an organ as small as the mouse thyroid without influencing it significantly. The beta rays, with a maximum range in tissue of about 2 millimeters, give up much of their energy within the gland, although a considerable amount is carried beyond the thyroid limits (24). The central part of the thyroid is subjected to the largest amount of radiation, hence the maximum injury, since it receives radiation from all the peripheral regions.

The progressive loss of radioactivity from the thyroid which occurs after a single dose of radioiodine results from the redistribution of I^{131} in the body, and its excretion, as well as from the natural decay of the isotope. The term "effective half-life" of I^{131} refers to the overall rate of loss of radioactivity from the thyroid. For the mouse the effective half-life of I^{131} after a dose of 200 microcuries is 1.25 days (14).

Effects on maternal thyroid. Extensive damage to the maternal thyroid resulted from the administered radioiodine, as has been reported in previous studies by others. Distinct histological changes in the gland were observed in animals autopsied 3 days after injection. The principal pathological effects consisted in destruction of follicles, with distortion of the epithelial nuclei and vacuolization of the cytoplasm. Coincident with the epithelial necrosis there occurred a marked inflammatory reaction with heavy leucocytic infiltration. These changes were most pronounced in the central part of the gland (Fig. 3). The parathyroid glands appeared undamaged.

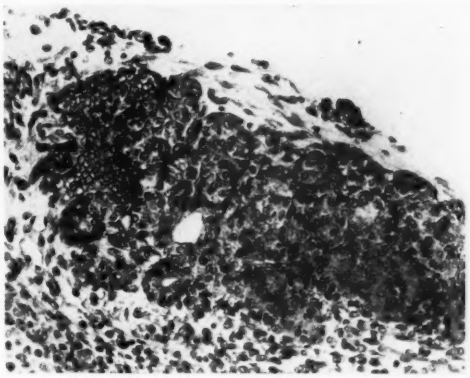

Fig. 2. Thyroid of 17 day fetal mouse, showing follicles. Some of these contain small amounts of colloid.

Fig. 3. Thyroid of adult mouse 3 days after a single dose of 200 microcuries of I^{131}. Necrosis of follicles and inflammatory reaction are evident in center of section.

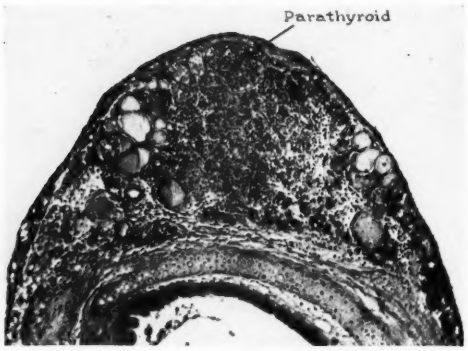

Fig. 4. Thyroid of adult mouse 13 days after a single dose of 200 microcuries of I^{131}. Necrosis and inflammatory reaction are more advanced. There is a heavy deposition of fibrin in the central part of the gland, and only a few follicles remain around the periphery. The inner aspect of the parathyroid has also been damaged.

Histologic examination of the thyroid of maternal animals at later stages following treatment showed progressive injury. At 2 weeks almost all of the follicles were destroyed, only a thin rim of recognizable thyroid tissue remaining at the periphery of the gland (Fig. 4). The epithelial lining of even these follicles appeared severely damaged, consisting either of a thin, acellular membrane or of one containing only a few pyknotic nuclei. The central, most severely damaged, part of the gland contained inflammatory cells and large amounts of fibrin undergoing organization. The centripetal, inner aspect of the parathyroid glands also revealed evidence of similar injury. By the third week after injection of radioiodine, fibrosis and hyalinization of the thyroid were well established (Fig. 5).

This profound anatomical damage to the thyroid led to corresponding alterations in its functional capacity. The administration of tracer doses of radioiodine to a group of mice at biweekly intervals following a single large dose of 200 to 400 microcuries of I^{131} revealed only slight uptake of iodine (2 to 6 per cent) by the thyroid after the initial damage. Prior to this the gland retained 20 per cent to 25 per cent of administered radioiodine.

Effects on offspring. Growth. The offspring of mice injected with radioiodine before the 16th day of pregnancy were indistinguishable from the controls in respect to growth, development, general appearance, and behavior. There was likewise no significant difference in mortality between the two groups. Distinct deviations from normal were observed in the offspring of animals injected after the 16th day of pregnancy. Although their birth weight was similar to that of the controls, the experimental animals grew more slowly, their growth curve lagging behind that of the control litters. Size differences were apparent in some animals by the 10th day of life (Fig. 6). At the age of 2 months the offspring of mothers injected on the 17th day of pregnancy averaged but 27.4 grams, 13 per cent less than the 32.8 gram average of the controls. The fur

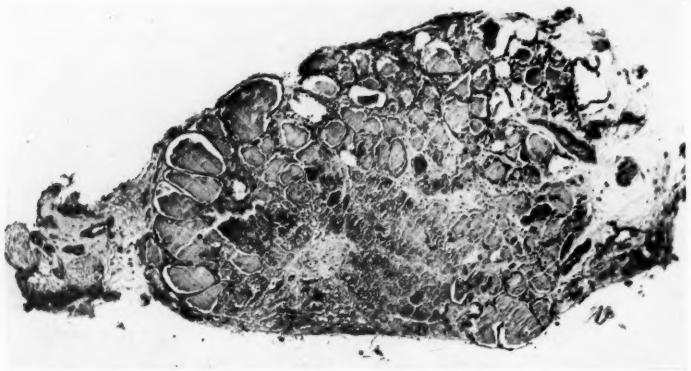

Fig. 5. Thyroid of adult mouse 20 days after a single dose of 200 microcuries of I^{131}, showing beginning fibrosis.

of several experimental animals was sparse and shabby, especially in the head and neck region. In a few instances areas of alopecia were observed, with superficial ulceration of the skin. No conclusions can be drawn concerning the relative mortality in the experimental and control groups, because sickly animals were usually killed for autopsy.

Breast tumors. By the age of 1 year about 15 per cent of the surviving animals had developed mammary adenocarcinomas. This is in keeping with the anticipated incidence of spontaneous mammary tumors in this strain of mice, and is without significance for the present experiments.

Fertility. The procreative ability of the offspring born to mothers treated on the 17th day of pregnancy was tested by two sets of mating experiments. At age 10 months a group of experimental male mice were mated with control females; and a group of experimental females were mated with control males. In each case, 1 male was caged with 3 or 4 females for 12 days.

Six experimental males sired a total of 15 litters (averaging 9 young per litter) among 17 control females. Only 2 of the females failed to conceive. Two control males sired 3 litters (averaging 6 young per litter) among 7 experimental females. Another mouse died while pregnant and the remaining 3 failed to reproduce. These observations indicate normal reproductive performance among the male offspring of radioiodine-treated mothers and would attest adequate gonadal function. The somewhat inferior record of the female offspring is in accord with Gorbman's experiments with adult mice. More than 300 of his females produced a total of only 9 litters within 5 months after treatment with I^{131}. Histologic examination of their ovaries revealed an absence of ova in most of the animals—an effect similar to that produced by x-rays.

Thyroid. Pathological alterations in the thyroid and pituitary glands of the offspring of radioiodine-treated mothers were of special interest. The thyroids developed normally in the 10 autopsied young of mothers injected before the 16th day and were indistinguishable from the controls. Distinct retardation of

Fig. 6. Young mice at 10 days of age showing effects of exposure to I^{131} in utero. Mouse on right born to mother who was treated on 17th day of pregnancy with 200 microcuries of I^{131}. Control on left.

glandular development was observed in the offspring when the I^{131} was administered on the 17th day, however. By the 10th day of neonatal life, the thyroid gland of normal control mice is well developed and contains distinct colloid-filled follicles (Fig. 7). The glands of the 3 experimental offspring autopsied at this age were much reduced in size, their follicles only a fraction of the normal dimensions, with a corresponding diminution in colloid content (Fig. 8). Many follicles appeared completely collapsed or contained only a tiny lumen with no colloid.

At 3 months of age the thyroids of 3 experimental young presented a pattern of injury which resembled that sustained by the mater-

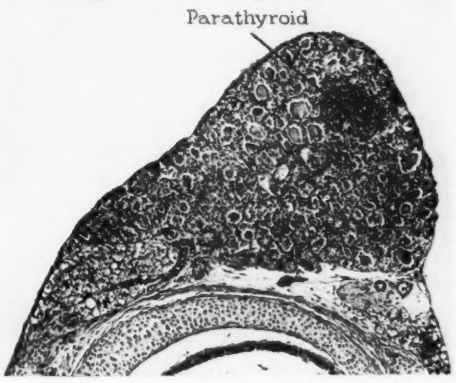

Fig. 7. Thyroid of control mouse aged 10 days.

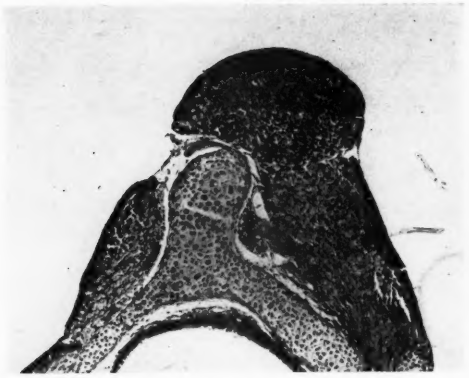

Fig. 8. Thyroid of experimental mouse aged 10 days. Mother was treated on 17th day of pregnancy with 200 microcuries of I^{131}. Follicles are shrunken and gland is fibrotic. Same magnification as Figure 7.

Fig. 10. Thyroid of experimental mouse offspring aged 3 months; showing effects of I^{131} acquired in utero. Damage to follicles and fibrosis are maximal in central part of gland. Same magnification as Figure 9.

nal gland after I^{131}. Damage was greatest in the central region of the thyroid, where the follicles were collapsed, the cells shrunken, and their nuclei pyknotic. The surrounding peripheral parts of the gland consisted of colloid-containing follicles of different sizes and in various states of preservation. Figure 10 shows a typical section depicting these changes, for comparison with a normal control of the same age (Fig. 9).

Despite this clear histological evidence of thyroid injury in the experimental offspring, later functional studies failed to reveal any depression of the gland's ability to concentrate iodine. At the age of 5 months the average uptake of I^{131} following the administration of a tracer dose to 3 experimental animals was 17 per cent, whereas 3 control mice of the same age had an I^{131} uptake of 13 per cent. This normal uptake is believed to result from the regenerative processes which eventually followed I^{131} injury to the thyroid, and for which there is abundant histologic evidence in the glands of animals autopsied at later stages.

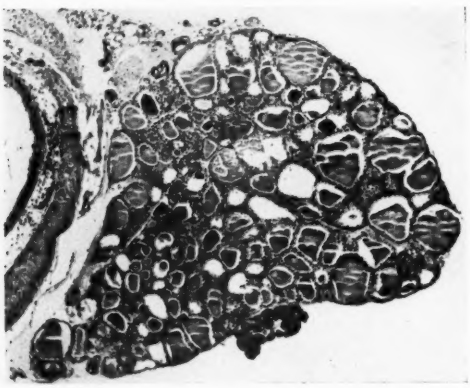

Fig. 9. Thyroid of control mouse aged 3 months.

By the age of 9 to 12 months a variety of pathologic changes had developed in the thyroids of the 10 autopsied experimental offspring. These were of three distinct types: fibrotic, hyperplastic, and degenerative. The fibrotic changes are well illustrated in Figure 11. The central part of the gland has been replaced completely by scar tissue and only in the extreme peripheral regions are remnants of thyroid tissue recognizable. Figures 12 and 13 show sections of glands in which the hyperplastic changes are predominant. These sections contain actively proliferating thyroid epithelium growing in cords or in compactly arranged follicles, which contain virtually no colloid. In Figure 12, to the right of the main mass of the gland and extending into the region of the thyroid isthmus, are isolated pale-staining cells, some of which are vacuolated, remnants of previously damaged thy-

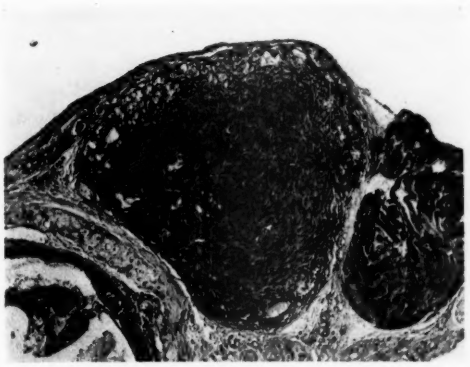

Fig. 11. Thyroid of experimental mouse offspring at 1 year, showing extreme fibrosis of gland with almost complete destruction of follicles.

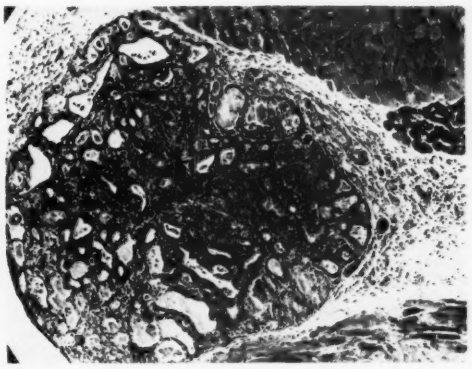

Fig. 12. Thyroid of experimental offspring at age 9½ months, showing compensatory hyperplasia. There is beginning formation of small adenomas.

roid epithelium. Some of the glands presented a nodular surface, as shown in Figure 14. On section the thyroid can be seen divided unevenly into distinct masses of hyperplastic tissue by connective tissue septa. In common with the pathologic appearance of thyroid hyperplasia in the human, many of the mouse sections contained areas in which papillary projections of hyperplastic epithelium extended into the lumens of the follicles (Fig. 15). A final variant, often seen in conjunction with hyperplasia, namely degeneration, is also illustrated in Figure 15. Several of the follicles, markedly dilated, contain exfoliated epithelial cells and macrophages laden with hemosiderin. Occasional mitotic figures were present in all of the specimens presenting the varieties of hyperplasia described previously.

The final phase of pathologic change in the thyroid of the experimental offspring is the counterpart of colloid goiter in the human. The mouse gland was enlarged to about twice its normal size, its surface lobulated. On section, the thyroid consisted of very large, colloid-filled follicles lined with flattened epithelium. The cells had poorly defined outlines and contained dark-staining nuclei (Fig. 16). This probably represents an end stage in the processes of hyperplasia and the ensuing epithelial involution. In some specimens the areas of hyperplasia and colloidal exhaustion can be seen side by side (Fig. 17). These developments are consistent with Marine's conception of accumulation of colloid and the formation of goiter as a natural sequel to hyperplasia and the establishment of physiologic compensation.

Radioautographs of thyroid sections in animals of this series between the ages of 9 and 12 months showed uptake of the element by the hyperplastic glandular tissue, with little or no activity present in the epithelium comprising the greatly dilated colloid-containing follicles.

Similar changes occurred in the thyroid glands of another series of 12 mice, aged 1 year, whose mothers were injected with I^{131} on the 18th day of pregnancy.

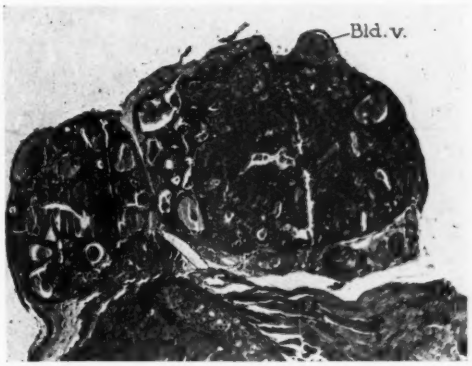

Fig. 13. Thyroid of experimental offspring at age 1 year, showing nodular hyperplasia. Note thickened walls of blood vessels.

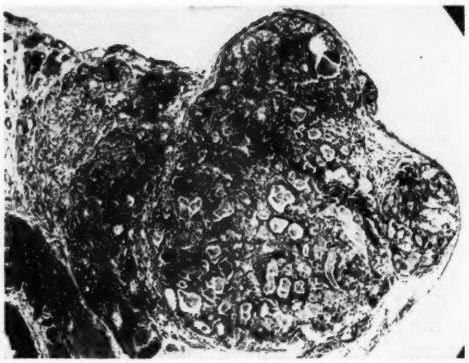

Fig. 14. Nodular hyperplasia in experimental offspring at 9½ months.

Pituitary gland. The pituitaries of a total of 32 mice of about a year's age were studied. After removal of the calvarium and brain the entire skull was immersed in Bouin's solution for fixation. Examination of the pituitaries under the binocular dissecting microscope revealed significant enlargement of the gland in one-third of the mice whose mothers were injected on the 17th or 18th day of pregnancy. All but 1 of the enlarged glands contained hemorrhagic areas which were grossly visible on the dorsal surface. The pituitary was then dissected out under the binocular dissecting microscope, fragments of adhering dura were trimmed away, and the gland was weighed immediately on a torsion balance. After careful orientation of the gland serial sections were cut in the frontal plane. Histologic study was made following staining by a variety of techniques, including hematoxylin and eosin, Masson's trichome stain, and Schiff periodic acid reagent.

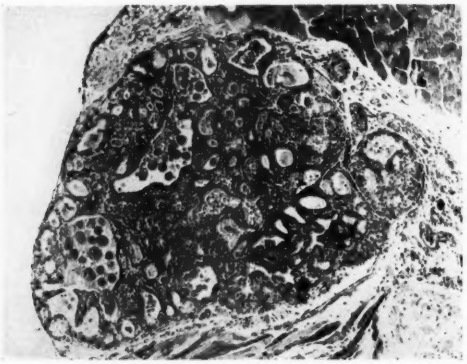

Fig. 15. Thyroid of experimental offspring at 10 months. Hyperplasia has resulted in formation of small adenomas. Degenerative changes are also in evidence, with dilatation of some follicles and exfoliation of cells into lumens.

The pituitary weights are listed in Table IV. The glands of 3 animals whose mothers were injected on the 15th day of pregnancy appeared normal and were within the weight range of the 11 controls. Two tumors (only 1 of which was weighed) were found among the 6 animals examined in the 17 day series and 4 tumors were discovered among 12 offspring of mothers injected on the 18th day of pregnancy, 2 in males and 2 in females. The largest of the weighed tumors was 59.1 milligrams, in comparison to an average normal gland weight of 2.17 milligrams for the controls. No correlation could be established between the presence or absence of pituitary tumors and the histologic appearance of the thyroid.

On histologic examination the tumors were found confined to the anterior lobe, which had displaced to the periphery and markedly compressed the pars intermedia and the pars nervosa (Figs. 18 and 19). The tumors were composed of chromophobe cells arranged in cords and in solid sheets (Fig. 20). Many of the cells were in the process of mitosis. Small numbers of basophils and eosinophils were present at the periphery of the tumor.

DISCUSSION

The correlation of functional activity of the fetal thyroid with specific changes in its structural development constitutes a significant advance in the field of endocrine embryology. Chapman and others (3) applied the tracer technique to this problem by the administration of small doses of I^{131} to human patients prior to therapeutic abortion. The quantitative aspects of the subject have been elaborated in greater detail in the present work on the mouse. The striking point of agreement in both studies is the temporal correlation between iodine uptake and histologic differentiation of the thyroid. In the human these occur relatively early in pregnancy, at the 14th week. In the mouse, by contrast, specific thyroidal differentiation and behavior become

detectable for the first time between the 16th and 17th days, a relatively late stage in the 20 day gestation.

Accurate estimation of the radiation dosage received by the maternal thyroids in these experiments is not possible. In the elongated mouse thyroid of 4 milligrams, 20 per cent uptake of 200 microcuries of I^{131} with an effective half-life of 1.25 days would result in a maximum dose of the order of 200,000 equivalent roentgens while the minimum dose, at the ends of the gland, might be only one-tenth of this or even less. Thus the amount of thyroid radiation received by the maternal mice is within the range used in thyroid cancer therapy in the human but is more than ten times the dose used in hyperthyroidism.

This quantity of radiation produces severe damage to the adult mouse thyroid, as has been shown in this and in previous studies. The present experiments have also demonstrated that radioiodine administered in late pregnancy results in certain deleterious effects on the offspring. Retardation of growth was observed by about the 10th day of life. Most noteworthy were specific morphologic alterations in the thyroid and in the later appearance of chromophobe adenomas of the pituitary.

The postnatal pathologic alterations in the thyroid apparently resulted directly from radiation damage inflicted by I^{131} taken up by the thyroid *in utero*, and not by hormonal or other indirect mechanisms. First, no damage occurred in the thyroids of offspring of mothers treated before the 16th day of pregnancy, i.e., before specific uptake of iodine by the fetal gland. Second, the early pattern of injury was identical with that which follows direct uptake of I^{131} by the adult thyroid, with maximal damage in the central region of the gland. It is unlikely that significant additional I^{131} uptake by the thyroid occurred after birth as the result of its excretion in the maternal milk (30). Rugh has shown that the I^{131} activity of the blood and milk of the mouse drops to a low level which is quite insignificant for the nursling, by 24 hours after the administration of 200 microcuries to the mother.

A recapitulation of the sequence of events involving the thyroid would be as follows:

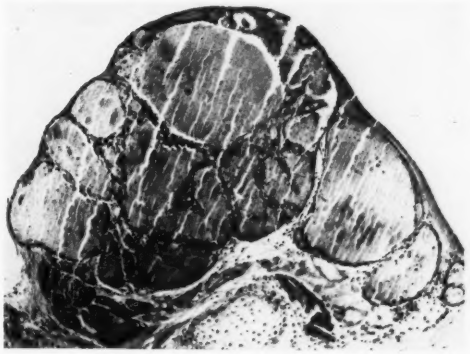

Fig. 16. Colloid goiter in experimental offspring at 10 months.

(1) deposition of I^{131} in the fetal thyroid, (2) fibrosis and retardation of its early postnatal development, (3) compensatory hyperplasia, resulting in nodular adenomas, (4) degeneration, with exfoliation of thyroid epithelial cells, and dilatation of follicles, leading to (5) colloid goiters. Compensatory hyperplasia in the thyroid has been observed in human patients who have been treated with radioiodine (4). Nodular adenomas and colloid goiters, however, as developed in these experiments, have not been reported previously from I^{131} injury in humans or in animal studies. Gorbman (14) has seen no evidence of thyroid regeneration in adult mice after severe injury with I^{131}. The changes described

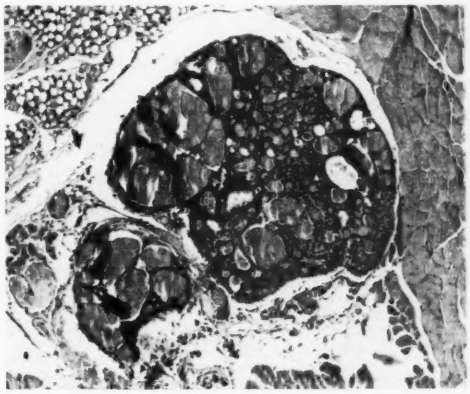

Fig. 17. Coexistent hyperplastic thyroid tissue and colloid goiter in experimental offspring aged 1 year.

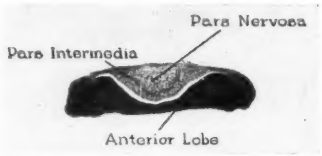

Fig. 18. Control mouse pituitary.

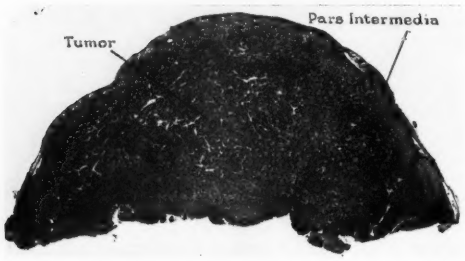

Fig. 19. Pituitary of experimental offspring at 1 year, showing tumor. Same magnification as Figure 18.

in the present experiments therefore appear to be related specifically to injury received by the fetal thyroid *in utero*. Similar thyroid adenomas in adult rats, produced by treatment with the goitrogenic agent in Brassica seeds (16), have been attributed to long continued stimulation by excessive amounts of thyroid stimulating hormone.

A transient hypothyroid state in the young is suggested by their retarded growth during the neonatal period, although faulty maternal lactation may have been a contributory factor. That the metabolism of the offspring was

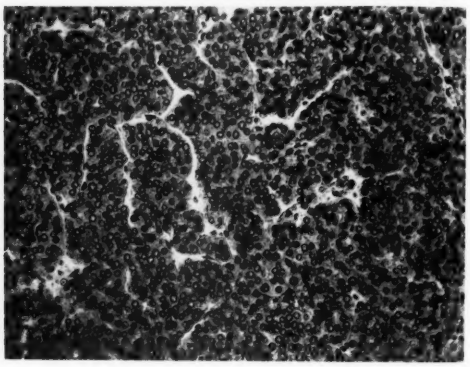

Fig. 20. High power view of chromophobe tumor in Figure 19.

TABLE IV.—PITUITARY WEIGHTS OF OFFSPRING

No.	Day of pregnancy injection I^{131}	Pituitary		Sex
		Weight	Tumor	
1	15	3.01*		F
2	15	2.35*		F
3	15	2.10*		M
4	17	59.1	+	
5	17	(not weighed 4x4x2 mm.)	+	
6	17	2.48		
7	17	2.35		
8	17	2.86		
9	17	2.96		
10	18	22.7 *	+	F
11	18	14.1 *	+	F
12	18	13.8 *	+	M
13	18	31.4 *	+	M
14	18	2.30*		F
15	18	2.54*		F
16	18	2.32*		F
17	18	1.40*		F
18	18	2.06*		M
19	18	1.90*		M
20	18	1.07*		M
21	18	1.43*		M
22	Control	4.00		
23	Control	2.42		
24	Control	2.54	Av. 2.79	
25	Control	2.65		
26	Control	2.34		
27	Control	1.84*		M
28	Control	1.51*		M
29	Control	1.62*		M
30	Control	1.74*	Av. 1.65	
31	Control	1.53*		
32	Control	1.65*		

*All pituitaries were fixed in Bouin's solution for only a few minutes before weighing, except the specimens marked by an asterisk, which were fixed for 10 days prior to weighing.
+Indicates presence of tumor.

normal later is indicated by a normal uptake of tracer doses of I^{131} and by normal reproductive performance, at least among the males. The possibility of selective damage to the female gonads by radioiodine received *in utero* is now being investigated.

Spontaneous tumors of the pituitary are very rare in mice. Maude Slye discovered

only 1, an "infiltrating adenoma," in 11,188 mice which she autopsied and she was able to find no others reported in the literature. More recently Dickie and Woolley (7) have observed basophil adenomas in certain hybrid mice that were castrated at birth. Chromophobe adenomas have been found in mice only after prolonged estrogenic stimulation (1, 6, 10, 11, 36). They do not occur spontaneously. The appearance of chromophobe adenomas in mice following treatment with I^{131} therefore relates these tumors causally to the radioactive isotope. Gorbman (13, 14) discovered pituitary tumors 250 days or more after treatment of adult mice. The present experiments have shown that identical tumors result from I^{131} received *in utero*. Rugh has recently made similar observations in nursling mice which received I^{131} in the maternal milk. Gorbman was able to correlate the size of the tumor with the dose of I^{131} and Rugh made a similar correlation between the amount of I^{131} received in the milk by the nurslings and the incidence of subsequent tumor development.

The mechanism of production of pituitary tumors in mice treated with radioiodine remains obscure. Reduction of the thyroxine level in rats, whether by thyroidectomy, antithyroid drugs, or I^{131}, leads to an increase in the proportion of the pituitary basophils (12, 17), a change which has been observed also in this work. This sheds no light, however, on the chromophobe tumors.[1]

In a human patient who was autopsied 19 days after treatment with I^{131}, the pituitary contained the second greatest amount of activity in the body, 3 per cent of that of the thyroid (2). We have been unable to confirm this observation in mice. The pituitaries and thyroids of 3 animals were removed and their activity measured 24 hours after a dose of 200 microcuries of I^{131}. There was no selective concentration of the element by the pituitary, in contrast to the thyroid. This finding lends no support to the view that the chromophobe adenomas are caused by direct irradiation by I^{131} trapped in the gland. Radioiodine which is taken up by the thyroid is incorporated into thyroxine which the gland synthesizes. The circulating radioactive hormone, acting reciprocally on the anterior pituitary, subjects the gland to irradiation. There is some selective concentration of thyroxine in the pituitary (5), but calculations indicate that the amount of radiation thus delivered to the gland is so small that it is unlikely to be tumorigenic. Similarly the amount of gamma radiation received by the pituitary from I^{131} in the thyroid is probably insignificant.

The extent to which these experimental observations are applicable to clinical problems in the human is a matter of uncertainty. It has been established (3) that the thyroid of the human fetus is already able to concentrate I^{131} at 14 weeks. Rate of uptake of the element increases progressively with fetal development. The present experiments have shown that the mouse fetus, although retaining less I^{131} than the adult, is not immune to the damaging effect of its radiations. In the absence of knowledge that the human fetus reacts differently to radioiodine, it would scarcely seem justifiable to treat pregnant human patients with this potent substance after the first trimester if an alternative method of therapy can be used.

SUMMARY

1. Pregnant mice were injected with single doses of radioiodine at various stages of pregnancy.

2. The radioactivity in the fetus was measured 48 hours later. Iodine concentration in the fetus occurred in animals injected on the 16th day of pregnancy but not earlier. This corresponds with the stage of development at which follicles begin to appear in the fetal thyroid. The rate of uptake of I^{131} increased rapidly as term was approached.

3. Neonatal growth was retarded in young born to mothers injected with radioiodine on or after the 17th day of pregnancy.

4. Later reproductive performance was normal in the male offspring, possibly impaired in the female offspring, of the I^{131} treated mothers.

5. Specific pathological changes occurred in the thyroids of the offspring. These changes

[1] In a recent study by Goldberg and Chaikoff (*Endocrinology*, 1951, 48, 1-5), pituitary tumors in the mouse were prevented by feeding desiccated thyroid following the administration of I^{131}. The authors therefore ascribed these tumors, which they believe to be of basophil rather than chromophobe origin, to hypothyroidism.

consisted of fibrosis, later compensatory hyperplasia with adenoma formation, and ultimately colloid goiters.

6. Chromophobe adenomas of the pituitary were discovered in one-third of the surviving offspring between the ages of 9 and 12 months.

7. The use of radioiodine in the treatment of pregnant human patients after the first trimester is considered unwise in the light of present knowledge, if the therapeutic objective can be attained by other methods of treatment.

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HEMOGLOBIN SPREADING TEST DURING PREGNANCY

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ACCORDING to Venning, pregnancy can be divided into 3 periods in respect to the excretion rate of urinary hormone metabolites. The first trimester is mainly characterized by a marked increase in the excretion of gonadotropins and corticoids. After this initial rise, both urinary corticoids and gonadotropins return to normal levels. During the third period, an increased output of corticoids, folliculoids, and pregnandiol is observed. It should be pointed out that the urinary excretion of corticoids shows a double peaked curve, one maximum coinciding with the peak of the gonadotropin excretion and a second which corresponds to the onset of the placental function. The level of these metabolites seems closely related to the secretion of this organ. It is well known that the placenta is an important source of gonadotropins and of various folliculoids. Venning has excluded the participation of fetal adrenals, suggested by Samuels and co-workers, because little or no cortical activity is found in the urine of infants in the early days of life. Moreover, from the work of Knowlton and Jailer (5), the placenta might elaborate corticoids and probably ACTH which could account for the rise in urinary cortical substances during pregnancy.

It has been shown previously that corticoids, folliculoids and gonadotropins exert a definite action on the spread of an intradermally injected dye. The spread is dependent on numerous factors, the most important being Duran-Reynals' spreading factors. The hyaluronidase acting on hyaluronic acid in the mesenchymal ground substance is the best known, but it is beyond doubt that, apart from hyaluronidase, numerous enzymatic and non-enzymatic factors are involved in the spread mechanism. The relationship between spread and cortical hormones was pointed out by Menkin and Opsahl (8). In previous experiments we have shown that cortisone significantly inhibits the spread while desoxycorticosterone acetate, lyophilized anterior pituitary, somatotropic hormone (growth hormone) and thyroxine enhance it (3). The dose of desoxycorticosterone acetate is important since small quantities do not exert any significant influence (Opsahl, 9). Estrogens and gonadotropins act in decreasing and increasing respectively the permeability of the ground substance (Lurie, Sprunt). Lurie suggested, however, that by inducing the adaptation syndrome of Selye, the action of estrogens could be mediated through the adrenals. This assumption seems to be correct, since estrogens fail to inhibit hemoglobin spread in adrenalectomized rats (2).

Our aim was to investigate in the rat the spread of a hemoglobin spot during pregnancy and possibly to correlate the hormonal changes normally occurring during pregnancy with alterations in spreading.

MATERIAL AND METHODS

Thirty-eight albino female rats weighing 200 grams were divided into two groups. The animals of the first group (10 rats) were used as controls. The remaining 28 were mated and the date of mating was established by the microscopical finding of spermatozoids in the vaginal smears.

After 1, 6, 8, 9, 14, 19, 20 days of pregnancy and a few hours before delivery, 0.2 cubic centimeter of a 15 per cent solution of hemoglobin was injected into the posterior region of the back, which area had been depilated the previous day. The surface of the spot was measured 2½ hours later and the area was calculated by the following formula:

$$S = \pi \frac{\text{larger diameter} \times \text{smaller diameter}}{4}$$

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Dr. Ducommun is a Fellow of the Swiss Academy of Biology and Medicine; Dr. Timiras, a Fellow of the Canadian Life Insurance Officers Association, and Dr. Dordoni, a UNESCO Fellow (Canada).

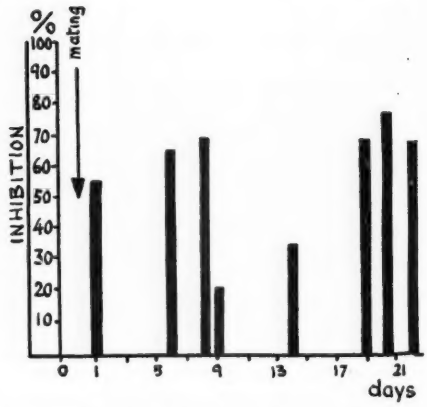

Fig. 1. Hemoglobin spreading test during pregnancy.

The controls were injected by the same procedure at the same time intervals.

RESULTS

As seen in Figure 1, and Table I, hemoglobin spread is inhibited significantly the day after the successful mating. This inhibition is prolonged until the 9th day, at which time there is no difference between the spread in control and in pregnant animals. The inhibition reappears on the 19th day and remains unchanged till delivery.

DISCUSSION

Our results indicate a parallelism between the level of corticoids and the inhibition of the spread. The greatest inhibition was found during the first and the third periods of pregnancy. These observations can be compared with Venning's results in pregnant women. It is beyond doubt, however, that during pregnancy, other hormones do participate in the regulation of the spread. Gonadotrophins are known to enhance it (Sprunt). This effect seems to be completely counteracted by the corticoid-inhibiting action during the first period. During the third phase, the rise in the urinary corticoids is accompanied by a simultaneous increase in the excretion of pregnandiol and folliculoids. Lurie has shown that estrogens inhibit the spread; meanwhile, nothing is known about the action of progesterone. The inhibition which was observed during this phase can be related to both corticoids and folliculoids.

Although we do not know whether the observed relationship would hold in women, further clinical investigation along these lines would seem indicated. The response can be obtained very rapidly. The use of hemoglobin instead of other dyes prevents permanent staining of the skin. The test can be repeated several times in normal pregnant women and in pre-eclamptic stages. The subjects examined by this new test should be absolutely free of intercurrent diseases which increase the corticoids levels, as has been demonstrated by Browne and associates.

TABLE I.—SPREAD OF SUBCUTANEOUSLY INJECTED HEMOGLOBIN

Groups	Time	Surface sq. cm.	Inhibition—%
1	normal	6.5±1	0
2	1st day	2.9±1	55.4
3	6th day	2.3±0.3	64.7
4	8th day	2	69.3
5	9th day	5.2±0.14	20.0
6	14th day	4.4±0.16	32.4
7	19th day	2.07±0.2	68.2
8	20th day	1.5±0.2	77.0
9	delivery	2.1±1	67.7

No significant difference between groups 1, 5, and 6.
No significant difference between groups 5 and 6.

SUMMARY

The spread of subcutaneously injected hemoglobin was investigated during pregnancy in the rat. The inhibition of the spread was seen to be very high during the first and the third period. The use of this test is suggested for clinical purposes.

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EDITORIALS

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UNNECESSARILY RADICAL SURGERY

RECENT advances in surgery have led to a wider employment of radical surgical procedures, by reducing the mortality and morbidity associated with them. The increased safety not only permits resort to radical measures in patients who are poor risks, but also has been used to justify broader indications for such operations. Conspicuous examples of such procedures are the increased use of hindquarter and forequarter amputations for malignant melanoma or sarcoma of the soft tissues of the extremities.

These operations are recommended on the ground that in order to effect a cure it is necessary to remove the primary carcinoma, the regional lymph nodes, and the intervening lymphatics *en bloc*. This is in accord with the principles of radical cancer surgery established in the radical operations for cancer of the breast and of the colon and rectum. Basically, the assumption is made that the usual mode of lymphatic dispersion is by permeation; that is, a propagating tumor thrombus extending from the primary carcinoma continuously to the regional nodes. While this mode of dispersion may obtain in late stages of carcinoma, and exceptionally early in highly malignant tumors, it is well established that the usual mechanism of lymph node metastasis is embolic. Since this is the case, it is unwarranted to assume that the intervening lymphatic vessels harbor carcinoma and must be removed to effect a cure. If this were the case all two stage discontinuous operations would be doomed to failure; whereas actually the cure rate even after metastases are established is very satisfactory in such cancers as the lip and skin, where discontinuous two stage operations are the rule.

Success in two stage operations involves two considerations: an adequate removal of the primary lesion, based upon an accurate appraisal of its extent; and a complete removal of the regional lymph node metastases. Since the clinical diagnosis of early lymph node metastasis is inaccurate, a block dissection of the regional nodes is indicated. Failures are due to incomplete local removal of the primary carcinoma, inadequate dissections of the regional lymph nodes, or the existence of unsuspected or undetected blood borne metastases.

Radical amputations obviate the necessity for accurate appraisal of the local extent of the primary carcinoma, as well as the necessity for meticulous and time consuming conservative block dissections. Thus they hold the promise of greater probability of local control of the primary carcinoma, and

a more thorough eradication of the nodes possibly harboring metastases. These advantages are more than offset by the unnecessary mutilations and crippling which these operations produce. The surgeon's obligation must involve not only the saving of life but also the preservation of function. A more intensive application to the requirements of success in two stage conservative operations is preferable to the wider use of mutilating amputations.

Similar observations may be made in regard to the recent revival of one stage *en bloc* operations for oral cancer, combining radical neck dissection, jaw resection, and surgical eradication of the primary carcinoma. Here again success can be attained in many instances by eradication of the primary focus of disease, followed by a properly planned radical dissection, with preservation of the mandible. The mutilation and impaired function of the one stage procedure is avoidable in many cases, without seriously jeopardizing the prospect for cure. The fact that the radical operation can now be carried out without undue mortality does not in itself justify the indiscriminate use of this operation when more conservative measures are equally successful in properly selected cases.

GRANTLEY WALDER TAYLOR.

RUPTURE OF THE SPLEEN

THE usual clinical picture of a rupture of the spleen is quite well known and conforms to a definite pattern in history and treatment. There is a history of trauma to the abdomen, by direct blow or a fall, followed by a "latent period" of 6 to 10 hours in which the patient is symptom free, or has symptoms of a vague or indefinite nature, only to lapse into a sudden collapse from intra-abdominal hemorrhage. If the patient reaches the hospital reasonably soon, the diagnosis is usually made quickly and splenectomy is performed. If delay is encountered, the patient may expire.

What is not recognized today is that many patients are seen with multiple injuries, and the presence of a rupture of the spleen cannot be determined at once. The reason the diagnosis cannot be made early is twofold. First, the presence of multiple injuries, usually fractures, lacerations and contusions, requires immediate attention, and the possibility of intra-abdominal injury is not considered. Second, shock in varying degrees is present. One or more transfusions with other intravenous therapy are given, and the clinical evidence of intra-abdominal bleeding is masked. Not only are the signs and symptoms masked by the presence of shock but the bleeding may stop completely for a period of 1 to 6 days, after which time the hemorrhage may begin again with explosive suddenness. In rupture of the spleen with slow or intermittent intra-abdominal hemorrhage, the treatment of shock will support the blood pressure, the blood counts will remain close to normal, and the presence of intra-abdominal hemorrhage will not be suspected. Occasionally, one sees a case of multiple injuries in a patient in which shock and hemorrhage alternate, and only unusual alertness will lead to a proper interpretation of the true clinical state. It is only by adopting a routine policy of careful and repeated observation the first 24 to 48 hours, in all patients with multiple injuries, that one can make an early diagnosis of rupture of the spleen.

With the increase in the number of highway accidents, the automobile is becoming the most common instrument of trauma and injuries sustained as a result of this type of accident are usually multiple in character. The steering wheel, the dashboard, and the

back of a seat, are points that may produce trauma, and the abdomen is subjected to injury as well as the chest, head, and extremities. In a few cases there is a history of an automobile turning over, the patient is seen in the emergency room, and allowed to go home with a diagnosis of "multiple contusions and abrasions," only to return 4 to 6 days later, in shock from intra-abdominal hemorrhage. Trauma of this type, producing a rupture of the spleen, may be designated as the indirect type. In case the victim of the accident is a pedestrian, the injuries are more severe and the mortality much higher.

Approximately 25 per cent of the patients operated upon for traumatic rupture of the spleen, in the larger emergency hospitals in this country, can be classified as a direct-injury type of case. The direct-injury type of case is that small group of patients admitted with a history of a fall, or a blow to the abdomen or to the chest wall, with clinical findings of intra-abdominal hemorrhage. These patients are operated upon and the traumatized spleen, occasionally several fractured ribs, are the only injuries sustained as the result of the fall or blow. It is interesting to note the almost total absence of case reports of rupture of the spleen in baseball, basketball, football or other sports emphasizing the type of trauma that may produce a rupture of the spleen.

The diagnosis of a ruptured spleen is founded on certain signs and symptoms that rest securely on the presence of intra-abdominal hemorrhage. In those cases in which there is no intra-abdominal bleeding because of tamponade, or in which the bleeding is within the capsule of the spleen and not into the peritoneal cavity, the diagnosis can only be presumptive. The signs of intra-abdominal bleeding from a rupture of the spleen are tenderness and rigidity in the left upper quadrant of the abdomen. Additional symptoms that may or may not be present, depending on the character of the hemorrhage, are pain in the chest on deep breathing, and pain in the left shoulder (Kehr's sign). Abdominal pain, tenderness and rigidity in the left upper quadrant, and a positive Kehr's sign are the most common triad of clinical findings in the presence of a traumatized spleen. Two factors may add to confusion in making a diagnosis: the presence of injuries in the extremities or chest, which may lead the examiner away from the abdomen, or the spleen may have been fractured and hemorrhage into the abdomen may have been delayed. Blood counts have been found of little value in making a differential diagnosis, and in those few cases in which they do indicate a loss of blood the diagnosis of hemorrhage is obvious. Blood counts are of considerable value following splenectomy for rupture of the spleen to determine the amount of blood replacement needed. Repeated blood pressure determinations are of value, provided the patient is not in shock, but as many of these patients are being treated for shock the blood pressure level merely indicates the response of the patient to shock therapy. Diagnostic abdominal paracentesis, or "abdominal tap," can be used to great advantage in making an early diagnosis of rupture of the spleen, provided one understands the use of this procedure. One "abdominal tap" may be negative and as a negative tap does not rule out the diagnosis of rupture of the spleen it may be necessary to do a tap in each of the four quadrants of the abdomen. Patients have gone to surgery with a diagnosis of perforated ulcer, and acute appendicitis, only to have the surgeon find free blood in the peritoneal cavity and more extensive exploration reveal a ruptured spleen. The presence of some form of tamponade around the spleen will prevent the blood from reaching the free peritoneal cavity and lead to a negative abdominal tap.

A recent survey[1] of the problem of rupture of the spleen on the surgical services of the Los Angeles County General Hospital over a 10 year period (1936–1946) revealed some interesting findings. One hundred and one patients were splenectomized as an emergency surgical procedure, following an accident, in which there was trauma to the abdomen and chest. The over-all mortality was 16.8 per cent, with the highest rate occurring in those patients with multiple injuries. Two facts were obvious from this study: first, the type of the lacerations in the spleen, and second, the character of the intra-abdominal hemorrhage. The 101 spleens were classified according to gross pathology, as follows: single laceration, 15; multiple or stellate lacerations, 22; upper pole injury, 17; lower pole injury, 7; hilar or pedical laceration, 5; bisected spleen, 10; macerated spleen, 9; splenic tumor with rupture of the capsule, 16. A further classification of these cases can be made on the clinical basis of immediate hemorrhage and delayed hemorrhage. Seventy-four patients were operated upon within 24 hours following trauma and these were considered to have had immediate hemorrhage. Twenty-seven patients were operated upon 48 hours to 21 days following the trauma and they were considered to have had delayed hemorrhage. Immediate hemorrhage occurred in all cases in which there was a laceration of the spleen and the splenic capsule. In those cases in which the hemorrhage was intrasplenic with an intact capsule, the intra-abdominal hemorrhage was delayed. In 14 cases in which there were single or multiple tears through the capsule into the spleen, hemorrhage was delayed by some form of tamponade. Tamponade came about in three ways: a simple laceration of the spleen with the formation of a blood clot and temporary stoppage, single or multiple lacerations in which the omentum acted as a plug, and lacerations of the diaphragmatic surface of the spleen, with a walling-off of the hemorrhage by the stomach, colon, and omentum. Straining at stool, vomiting or coughing, or a full meal, will frequently furnish the mechanism to restart the hemorrhage. Microscopically, there was no evidence of a diseased spleen in the entire group; only parenchymal changes indicative of hematoma and hemorrhage were reported.

The usual clinical picture of rupture of the spleen in which there is a direct injury, followed by a latent period and then collapse, needs no comment. It is important to point out that patients with fractures and lacerations need an abdominal surgeon as well as an orthopedic and neurosurgeon. The abdominal surgeon must recognize the fact that multiple injuries may indicate a possible abdominal injury, and one of the most common is rupture of the spleen. The presence of shock in the patient will mask the symptoms the first 24 hours, while hemorrhage beneath an intact splenic capsule or some form of tamponade will delay intra-abdominal hemorrhage 2 to 21 days. In critical cases the use of a diagnostic abdominal tap will frequently help in making an early diagnosis. There is evidence to support the contention that spontaneous rupture probably never occurs in the normal spleen but that some form of trauma has occurred which the patient has forgotten.

RALPH V. BYRNE.

[1]BYRNE, RALPH V. Splenectomy for traumatic rupture with intra-abdominal hemorrhage. Arch. Surg., 1950, 61: 273-284.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE excellently illustrated monograph *Hepatostomia*[1] is a review of the surgical approach to hepatic drainage. It considers the subject from a historical background, dividing the topic into external and internal liver drainage. In the former the intrahepatic biliary system is drained to the exterior by means of anastomosis of the liver, either directly or indirectly to the skin, whereas in the latter the internal procedure involves an anastomosis with some part of the alimentary tract.

These procedures are exemplified by a discussion of 27 case histories in 25 of which the external technique is used and in 2 the internal procedure is employed. Cancer was the outstanding indication. The liver may be attached to the skin either directly or by means of a distant fistulous tract made of peritoneum, or by means of an indirect attachment using the gall bladder (hepatocholecystomia).

The internal hepatostomia is formed by anastomosis to the stomach, the duodenum, the jejunum or by forming a hepatocholangiogastrostomy, duodenostomy, or jejunostomy.

The volume is well organized, clearly written, and excellently illustrated to such an extent that it is possible to follow details of the anastomotic procedures without reviewing the text.

With the ever widening scope of liver surgery, the surgeon will do well to read and possess this succinct and well arranged monograph.

STEPHEN A. ZIEMAN.

THE book *Clinical Radiotion Therapy*[2] is a compilation written by 13 radiologists, 3 dermatologists, 2 surgeons, a urologist, and an internist. It presents the radiation therapy of both benign and malignant conditions. The pathological and clinical descriptions are unusually adequate for this type of work.

The change in the title of the second edition indicates its major change from the first edition which was entitled *Clinical Roentgen Therapy*. This is accomplished by adding the discussion of radium therapy to a revised description of the x-ray therapy in most sections. A supplement on dosage calculation in radium therapy and a supplement on low intensity radium needles by an authority on the subject are valuable additions.

There is, perhaps, a lack of emphasis on the modern concepts of tissue and tumor doses with the older concepts of skin and air doses still in predominance. Total dose is occasionally mentioned without mention of the all-important time over which the dose is to be given.

The book is well illustrated, attractively bound, and very much worth the time of anyone interested in radiation therapy. JOHN W. CLARK.

THE medical profession and especially the radiological group have anxiously awaited reports on *Supervoltage Roentgentherapy*[3] from the various radiological centers where special therapeutic techniques have been extensively employed. Indeed, it might be said that it is a privilege and a duty of such radiological centers to publish their results for the guidance of others in future endeavor, a duty which has been admirably fulfilled in this instance.

The authors recognize the necessity of a fundamental biological and clinical approach in the evaluation of supervoltage roentgentherapy. Two important considerations are involved: (1) the increased penetration of the higher voltage x-rays with reduction in peripheral scattering and consequent increase in depth dose, and (2) the increase in tolerance of the normal tissues to the quality of radiation generated at the higher voltages. Do they afford advantages from the standpoint of improved results?

The authors feel that the factor of increased penetration for many tumors has been overemphasized and that radiation of medium voltage which is almost universally available can be utilized successfully for many types of tumor provided there is an appropriate technique. However, some deep-seated lesions, e.g., esophageal carcinoma, seem to respond more satisfactorily to higher penetration. Differences in tissue tolerance with decreasing wave-length (higher penetration) have been considerably underestimated; the tissues withstand a higher dose of high penetration. As the final conclusion, the most one can expect thus far from supervoltage roentgentherapy is some improvement of results in those tumors which were previously known to be radiovulnerable, but the question raised is whether the improvement is in reasonable proportion to the economic and engineering difficulties entailed. Supervoltage radiation therapy has not fundamentally changed the concept of the clinical management of

[1] HEPATOSTOMIA. By Atilio J. Lasala and Manuel José Vazquez. Prologue by Professor Ricardo Finochietto. Buenos Aires: Lopez & Etchegoyen, 1950.

[2] CLINICAL RADIATION THERAPY. Edited by Ernst A. Pohle, M.D., Ph.D., F.A.C.S. Philadelphia: Lea & Febiger, 1950.

[3] SUPERVOLTAGE ROENTGENTHERAPY. By Franz Buschke, M.D., Simeon T. Cantril, M.D., and Herbert M. Parker, M.Sc, Springfield, Ill.: Charles C Thomas, 1950.

cancer by roentgentherapy as taught by the late Coutard, but there are certain definite indications for the higher voltage.

The authors state that to date radiation therapy for cancer of the breast is to be regarded as only an adjunct to surgery in selected cases, or a palliative measure in the treatment of metastases. Used alone it has its place in cases of advanced disease of the mammary gland for retardation of the growth or healing of ulcerating lesions. JAMES T. CASE.

IN a field of medicine as extensive as radiation therapy, in the light of present day developments, a monograph is a courageous undertaking. Such monographs have a decided value because of the fact that the author, unconsciously perhaps, allows himself to expand on certain topics, thus putting into the record details of protocol and results which might be missing in a work composed of contributions from specialists in all of the various branches of radiotherapy embraced in the all-inclusive title *Clinical Radiation Therapy*[1]. The international high esteem enjoyed by the author and his colleagues merits careful study of this monograph by all interested in the management of cancer and other affections in which radiotherapy plays a role. The style is inviting and the type and printing attractive. The numerous illustrations are helpful.

The reviewer is sure that the author and his colleagues fully recognize the necessity of estimating tissue doses and that such estimates have been taken into account in their practice but this kind of information is nearly absent in the text. In the preface, the author recognizes the omission of the depth-dose data but states that the system followed in the book is readily understood and reproduced by the general radiologist. We should emphasize, however, the fact that the feeling is growing rapidly that the time has arrived when radiotherapy should be applied only by radiologists with full understanding of the technique and importance of depth-dose measurement. Otherwise the book is up-to-date, with no serious omission detected in a careful perusal from cover to cover.

This kind of a text should be in the hands of every radiotherapist for frequent consultation. It is an excellent reference book for those who wish to keep informed as to what can be accomplished in the radiotherapeutic management of a multitude of affections. JAMES T. CASE.

REVIEW texts are gaining popular favor in the fast-moving pace of present day medicine and the British volume *Modern Trends in Obstetrics and Gynaecology*[2] compiled by Dr. Kenneth Bowes, will prove no exception. Designed as it is to review the newest ideas, trends, and concepts of these specialties, it is encyclopedic and in part loosely organized. It represents the contributions of over 70 different authorities from the British Empire and the United States, many of whom are biologists and pure scientists rather than clinicians. No item of knowledge or view tendered in the past 10 years is neglected, thus giving the book tremendous scope. It covers not only obstetrics thoroughly, gynecology less thoroughly, and surgery slightly, but also psychiatry, nutrition, and the social aspects of obstetrics and gynecology, intersexuality, fertility, x-ray, genetics, bacteriology, hematology, and all the loosely allied fields contributing to the specialty.

An excellent review is presented of the biology of menstruation with discussions of the work of Schlegel, Markee, and Smith and Smith. Equally helpful is the chapter on the pituitary gonadotropins and steroid hormones. Dr. A. T. Hertig's embryologic contribution with beautiful pictures of early human ova is well done. Dr. H. L. Sheehan's fine pathologic case studies highpoint the chapter on shock in obstetrics.

Medical obstetrics is emphasized throughout the compilation as exemplified by outstanding chapters on diabetes, pulmonary tuberculosis, heart disease, and anemia in pregnancy; and rather sparse sections on surgical management of obstetrics, and gynecologic problems. The chapters on genital tuberculosis, endometriosis, gynecologic pathology, anesthesia and vaginal cytology and abortion contain little new material and are disappointing.

Important recent works are well distilled for rapid assimilation: premalignant lesions of the uterine cervix—material which is drawn entirely from the American clinics; irradiation treatment of uterine cancer from Dr. J. Heyman's clinic, The Radiumhemmet, Stockholm; and the Rhesus factor in pregnancy. Unexpected inclusions are chapters on obstetric bacteriology, the law in relation to obstetrics and gynecology, and radioisotopes in research pertaining to obstetrics and gynecology.

The complete and up-to-date bibliography is limited almost entirely to the last decade except for classic monographs of a previous decade. It may prove a good reference book in view of its voluminous review character. The book is not designed for medical students or interns for it contains but a minimum of the fundamentals of clinical practice, but rather is designed to refresh the practitioner and to complement the academic obstetrician and gynecologist's fund of knowledge, and stimulate the research clinician in these fields. All this is done in a thoroughly readable, sometimes quasi humorous style characteristic of British medical writers.

J. C. MACMILLAN.

THE author of *Plasma Clot Suture of Peripheral Nerves and Nerve Roots*[3] has done many experi-

[1]CLINICAL RADIATION THERAPY. By Ira J. Kaplan, M.D., F.A.C.R. 2d ed. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1949.

[2]MODERN TRENDS IN OBSTETRICS AND GYNAECOLOGY. Edited by Kenneth Bowes, M.D., M.S.(Lond.), M.B., Ch.B.(Liverpool), F.R.C.S. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, 1950.

[3]PLASMA CLOT SUTURE OF PERIPHERAL NERVES AND NERVE ROOTS; RATIONALE AND TECHNIQUE. By I. M. Tarlov, M.D, Springfield, Ill.: Charles C Thomas, 1950.

mental and clinical studies using the plasma clot method of nerve union. During the past decade a large number of publications dealing with this work have appeared in the literature. This concise book is an excellent summary of the author's experience and contains numerous well selected drawings and photographs which portray the technique either devised or modified by Tarlov and his associates.

The author has added new tools to the field of peripheral nerve surgery. The use of plasma as a substitute for silk or tantalum suture is a relatively recent contribution. Although it is not original with the author, he has devised the latex molds and special air foam nerve holders so that neural tissue could be handled less traumatically. He has applied this technique both to large nerves as well as small, including even cauda equina nerve roots. The portion of the book dealing with the use of cable grafts is interesting and helpful for it deals with the difficult problem encountered in cases which have a defect too large to be bridged by end-to-end suture.

Not all readers may share the author's enthusiasm for plasma clot suture because the technique can at times prove cumbersome. Silk and tantalum sutures have not been completely replaced because these agents are used as adjuncts where tension exists.

This small volume is to the point and convincingly written. It should be valuable to the surgeon who desires a guide to the indications and technique for this type of nerve repair. DANIEL RUGE.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

THE DIAGNOSIS AND TREATMENT OF ADRENAL INSUFFICIENCY. By George W. Thorn, M.D., M.A. (Hon.), LL.D. (Hon.). 2d ed. Springfield, Ill.: Charles C Thomas, 1951.

TUMORS OF THE EYE. By Algernon B. Reese, M.D., D.Sc. (Hon.), F.A.C.S. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1951.

ANGEWANDTE UND TOPOGRAPHISCHE ANATOMIE; EIN LEHRBUCH FUER STUDIERENDE UND AERZTE. By Prof. Dr. G. Toendury. Stuttgart: Georg Thieme, 1951.

LEHRBUCH DER ROENTGENDIAGNOSTIK. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. 5th rev. enl. ed. No. 4, LIEFERUNG. Stuttgart: Georg Thieme, 1951.

PRINCIPLES AND PRACTICE OF OBSTETRICS. By J. P. Greenhill, M.D. 10th ed. Philadelphia, London: W. B. Saunders Co., 1951.

CHEST X-RAY DIAGNOSIS. By Max Ritvo, M.D. Philadelphia: Lea & Febiger, 1951.

LA TIROIODES Y SUS ENFERMEDADES. By Dr. J. H. Means. Buenos Aires: Editorial Artecnica, 1951.

CYSTEKTOMIE BEIM BLASENKREBS. By Prof. Dr. H. Boeminghaus. Stuttgart: Georg Thieme, 1951.

CLINICAL UNIPOLAR ELECTROCARDIOGRAPHY. By Bernard S. Lipman, A.B., M.D., and Edward Massie, A.B., M.D., F.A.C.P. Chicago: The Year Book Publishers, Inc., 1951.

SCOLIOSIS; PATHOLOGY, ETIOLOGY, AND TREATMENT. By Samuel Kleinberg, M.D. Baltimore: The Williams & Wilkins Co., 1951.

FIRST REPORT ON INSTITUTIONAL RESEARCH GRANTS OF THE AMERICAN CANCER SOCIETY. New York: American Cancer Society, Inc., 1951.

COMMITTEE ON GROWTH OF THE NATIONAL RESEARCH COUNCIL, FIFTH ANNUAL REPORT TO AMERICAN CANCER SOCIETY, INC., JULY 1949—JUNE 1950. Washington: Division of Medical Sciences, National Research Council, 1951.

SYMPOSIUM ON STEROIDS IN EXPERIMENTAL AND CLINICAL PRACTICE. Edited for the Committee on Arrangements by Abraham White. New York, Philadelphia, Toronto: The Blakiston Co., 1951.

LES XANTHOMATOSES. By A. L. Froehlich. Bruxelles: Les Editions. Acta Medica Belgica, 1951.

SURGICAL PATHOLOGY OF THE MOUTH. By E. Wilfred Fish, C.B.E., M.D., Ch.B., L.D.S. (Manch.), D.D.Sc. (Melb.), D.Sc. (Lond.), F.D.S., R.C.S. (Eng.). Philadelphia, London, Montreal: J. B. Lippincott Co., 1951.

ANATOMY IN SURGERY. By Philip Thorek, M.D., F.A.C.S., F.I.C.S. Philadelphia, London, Montreal: J. B. Lippincott Co., 1951.

GYNECOLOGIC CANCER. By James A. Corscaden, Ph.B., M.D. New York, Toronto, Edinburgh: Thomas Nelson & Sons, 1951.

THE PHYSIOLOGY OF THE NEWBORN INFANT. By Clement A. Smith, M.D. 2d ed. Springfield, Ill.: Charles C Thomas, 1951.

VISCERAL RADIOLOGY. By Emerik Markovits, M.D. New York: The Macmillan Co., 1951.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

HENRY W. CAVE, New York, *President*

ALTON OCHSNER, New Orleans, *President-Elect*

PRELIMINARY PROGRAM FOR THE 37TH CLINICAL CONGRESS—CIVIC AUDITORIUM, SAN FRANCISCO, NOVEMBER 5 TO 9, 1951

LETTERMAN Army Hospital has been selected as the source of the telecasts of surgical procedures for the color television program which will be a feature of the thirty-seventh annual Clinical Congress of the American College of Surgeons in San Francisco, November 5 to 9. The color telecasts will be shown at the Civic Auditorium, in which many of the other sessions of the Congress, and the scientific and technical exhibits, will be held.

Ciné clinics and postgraduate courses in specific surgical subjects will be other relatively new attractions. An extensive and varied program of operative clinics and demonstrations in 26 hospitals is being developed by the surgeons of San Francisco and of East Bay communities.

Other sessions planned are forums on fundamental surgical problems; a clinicopathological conference; symposia on cancer, on trauma, and on graduate training in surgery; evening sessions for general surgeons, ophthalmologists, and for otorhinolaryngologists; panel discussions for general surgeons and for surgical specialists; hospital conferences; official meetings; and medical motion picture showings.

COMMITTEE ON ARRANGEMENTS

The San Francisco Committee on General Arrangements for the Clinical Congress is composed of the following Fellows:

*EMILE HOLMAN, *Chairman*
*THOMAS F. MULLEN, *Vice-Chairman*
*FRANK GERBODE, *Secretary*
*HOWARD C. NAFFZIGER, *Member, Board of Regents*

H. GLENN BELL
FREDERIC C. BOST
EDMUND BUTLER
LOREN R. CHANDLER
JOHN W. CLINE
ROY B. COHN
WHITFIELD CRANE
ALBERT D. DAVIS
LEON GOLDMAN
*BERT L. HALTER
DAVID O. HARRINGTON
FRANKLIN I. HARRIS
LEONARD D. HEATON
*ARTHUR J. HUNNICUTT
ALSON R. KILGORE
CARLETON MATHEWSON, JR.
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PAUL C. SAMSON
ROBERT A. SCARBOROUGH
HENRY H. SEARLS
HERBERT F. TRAUT
WILLIAM W. WASHBURN
HENRY M. WEYRAUCH
JOHN H. WOOLSEY

*Executive Committee

HOSPITALS AND HOSPITAL REPRESENTATIVES

The hospitals which will arrange clinics for the 1951 Clinical Congress, and the names of the hospital representatives, follow:

San Francisco
Children's Hospital—RUTH FLEMING
Franklin Hospital—FREDERICK S. FOOTE
French Hospital—ALBERT C. DANIELS
Letterman Army Hospital—WALTER H. MATUSKA
Mary's Help Hospital—EVERETT CARLSON
Mount Zion Hospital—SANFORD E. LEEDS
St. Francis Hospital—GERALD BROWN O'CONNOR
St. Joseph's Hospital—JOHN J. BAZZANO
St. Luke's Hospital—G. DANIEL DELPRAT
St. Mary's Hospital—EDMUND J. MORRISSEY
San Francisco Hospital—CLAYTON G. LYON
Shriners' Hospital for Crippled Children—FREDERIC C. BOST
Southern Pacific General Hospital—COLIN C. MCRAE
Stanford University Hospital—GUNTHER W. NAGEL
University of California Hospital—HORACE J. MCCORKLE
Veterans Administration Hospital—HENRY L. SILVANI

East Bay
Alta Bates Hospital, Berkeley—MALCOLM B. HADDEN
Children's Hospital of The East Bay, Oakland—DEXTER N. RICHARDS, JR.
Herrick Memorial Hospital, Berkeley—R. BRUCE HENLEY
Highland—Alameda County Hospital, Oakland—HARRY E. PETERS, JR.
Samuel Merritt Hospital, Oakland—GROSVENOR T. ROOT
Peralta Hospital, Oakland—EDWIN G. CLAUSEN

Permanente Foundation, Oakland—AUGUST L. BARITELL
Providence Hospital, Oakland—WILSON FOOTER
U. S. Naval Hospital, Oak Knoll, Oakland—CAPTAIN J. M. C. GORDON, Commanding Officer
Veterans Administration Hospital, Oakland—THOMAS O. LAKE

OFFICIAL MEETINGS

A meeting of the Governors of the College will begin with luncheon on Monday, November 5, and continue in the afternoon. There will be adjourned meetings of the Board of Governors on Wednesday morning and Thursday afternoon.

President Henry W. Cave of New York will deliver the Presidential Address at the Monday evening meeting at the Civic Auditorium. At the same session Dr. Alton Ochsner of New Orleans will be installed as President for the year 1951–52, Dr. Thomas H. Lanman of Boston as First Vice President, and Dr. Joel W. Baker of Seattle as Second Vice President. The Sixth Martin Memorial Lecture, to be presented by Dr. Paul B. Magnuson of Washington, D. C., will be the closing address on this program.

The annual Convocation will be held at the Civic Auditorium on the final evening, Friday, November 9, when fellowships will be conferred upon the Initiates of 1951 and recipients of the Honorary Fellowship. The program will conclude with the presentation of the Fellowship Address by Dr. J. Roscoe Miller, President of Northwestern University, Evanston, Illinois.

The annual meeting of Fellows of the College will be held on Thursday afternoon, November 8.

COLOR TELEVISION

Color telecasts of surgical procedures at Letterman Army Hospital will be shown daily during the Clinical Congress in a meeting room at the Civic Auditorium. Smith, Kline & French Laboratories of Philadelphia are again making the telecasts possible by providing their equipment which employs the CBS system of color television. The San Francisco demonstrations will be the third use of this popular teaching medium at Clinical Congresses of the American College of Surgeons.

CINÉ CLINICS

Ciné clinics will again be sponsored, as in Boston, by Davis & Geck, Inc. Surgeons from Texas to British Columbia are participating in the filming of surgical procedures to be shown at the San Francisco meeting. The advisory committee on programs has selected the subjects and the Committee on Medical Motion Pictures is correlating the filming. The clinics will provide a unique facility for studying new developments and current thinking of leading surgeons and surgical groups of the West.

The program will consist of a series of talks on specific surgical problems, each illustrated by specially prepared and edited color motion pictures demonstrating major points of the technique employed. While retaining all important features of the surgical clinic, this method extends the scope beyond traditional limits by permitting demonstration of procedures usually difficult or impossible to schedule electively, and by providing for better visibility than is possible at the usual surgical clinic presentation.

EVENING SCIENTIFIC SESSIONS

Surgeons and other specialists, recognized as authorities in their fields, will address scientific sessions to be held on Tuesday, Wednesday, and Thursday evenings. Concurrent sessions will be held each evening for general surgeons, ophthalmologists, and otorhinolaryngologists.

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The Forum on Fundamental Surgical Problems will again be featured in ten sessions in which there will be presented brief reports of original clinical and experimental observations relating to the broad aspects of general surgery and the surgical specialties. A large number of abstracts have already been received from which selection for presentation will be made by the Committee, of which Dr. Owen H. Wangensteen of Minneapolis is the chairman. As a result of the large demand for the volume *Surgical Forum* published by W. B. Saunders Company, which contained 106 papers in full and 58 others in abstract form, all of which were presented at the 1950 Clinical Congress, it is planned to publish the 1951 Forum papers in a similar volume.

PANEL DISCUSSIONS AND SYMPOSIA

General Surgery panel discussions will be held Monday through Thursday afternoons. For otolaryngologists, there will be discussion sessions on the afternoons of Tuesday, Wednesday and Thursday, and for ophthalmologists, there will also be three afternoon sessions, two of which will be color-television operative clinics. Friday afternoon will be devoted to concurrent panel discussion sessions for six special fields of surgery: orthopedic surgery, obstetrics and gynecology, urology, neurological surgery, thoracic surgery, and plastic surgery. In addition to two obstetrics-gynecology panel discussions on Friday afternoon, the Congress program this year will have three other sessions devoted to subjects in this field.

Symposia on trauma, on cancer, and on graduate training in surgery, are scheduled for presentation on the afternoons of Tuesday, Wednesday, and Thursday, respectively.

POSTGRADUATE COURSES

Postgraduate courses similar to those given in Boston hospitals at last year's Clinical Congress are being planned as a part of this year's Congress program and will be given in five San Francisco hospitals. The five fields in which courses will be given, and the Chairmen who have been appointed to plan these courses, are:

Management of Fractures. Chairman, FREDERIC C. BOST.
Preoperative and Postoperative Care. Chairman, VICTOR RICHARDS.
Cancer—Modern Diagnostic Methods. Chairman, ALSON R. KILGORE.
Obstetrics and Gynecology. Chairman, HERBERT F. TRAUT.
Vascular Diseases. Chairman, FRANK GERBODE.

MEDICAL MOTION PICTURE PROGRAM

The Committee on Medical Motion Pictures is now choosing films on general surgery and the surgical specialties which are to be shown in San Francisco. Films which have been recently produced should be forwarded to the College for immediate review as it is the policy to include in the Clinical Congress program only those films which were submitted in time to obtain approval by the Committee.

HOSPITAL CONFERENCES

The thirtieth Hospital Standardization Conference will convene during the first four days of the Clinical Congress. Hospital administrators, trustees, members of medical staffs, nurses, technicians, dietitians, and heads of the various hospital departments and their personnel, are invited to participate in the discussions at the conferences which will be directed by leading authorities in the hospital field. There will be four morning, four afternoon, and three evening sessions.

At the one-hour general assembly for surgeons and hospital representatives on the first morning there will be discussion of the status of the Hospital Standardization program.

General themes for the other session are tentatively as follows: Monday afternoon, "Hospitals of the Future—Organization, Architecture, Personnel, Prepayment Plans"; Tuesday morning, "Care of the Chronically Ill"; Tuesday afternoon, "The Surgical Service"; Tuesday evening, "Medical and Hospital Public Relations"; Wednesday morning, "Demonstration of Sterilization Technique"; Wednesday afternoon, "Nursing Services"; Wednesday evening, "Civil Defense"; Thursday morning, "Medical Records"; Thursday afternoon, "Trustee-Physician-Hospital Problems" and Thursday evening, "Forum on Trends in Hospital Administration."

No conferences will be scheduled on Friday so that hospital representatives may see the exhibits, television and other interesting features of the Clinical Congress, and visit San Francisco area hospitals.

EXHIBITS

Both scientific and technical exhibits will be housed in the Civic Auditorium. The scientific exhibits were so successful in Boston that the College is formulating plans to repeat them on a larger scale at the San Francisco Congress and applications are now being accepted by the committee on scientific exhibits, 40 East Erie Street, Chicago 11.

There will be the usual extensive display of surgical and hospital supplies and equipment by manufacturers and distributors. Included in the exhibit will be displays of new medical books and journals by leading publishers. Besides housing the exhibits, the Civic Auditorium will be used for the color television, ciné clinics, medical motion picture showings, scientific sessions, and hospital conferences, and for registration of both the surgeons and the hospital personnel.

ADVANCE REGISTRATION

Surgeons who wish to attend the Clinical Congress should register in advance. This will greatly expedite the procedure of registering. No registration fee will be charged Fellows whose dues are paid to December 31, 1950. For endorsed candidates, the fee will be $5.00. Non-Fellows who after individual consideration are permitted to register, will pay a fee of $10.00. No registration fee will be required of Initiates of the class of 1951. Official registration blanks, transportation information, hotel reservation forms, and other details have been sent to all Fellows.

HOTEL RESERVATIONS

It is desirable that hotel reservations be made as early as possible, and for this purpose the official reservation form should be completed and returned to the

San Francisco Convention Bureau
61 Grove Street, San Francisco 2, California

Ample first-class hotel accommodations have been assured so that registrants for the Congress need not fear the limitations of former years. It is important in any communication about hotel reservations that reference be made to the Clinical Congress of the American College of Surgeons.

All communications relative to housing should be directed to the San Francisco Convention Bureau and not to the hotels.

POST-CONVENTION TOUR

For Fellows who are planning to attend the Pan Pacific Surgical Conference, or who would like to have a vacation in Hawaii following the Clinical Congress, the College has arranged with Mr. R. R. Rickson, travel agent for the Matson Steamship Lines, to offer the following convention tours:

CONVENTION TOUR No. 1—27 days—round trip by steamer *Lurline* leaving Los Angeles Harbor November 14th, and returning to Los Angeles December 11th. All expense includes round trip steamer space, room with private shower. U. S. transportation tax, Royal Hawaiian Hotel on Beach at Waikiki (American Plan).....$745.55

CONVENTION TOUR No. 2—14 days—Outward by Stratacruiser from San Francisco November 10th, return by steamer *Lurline*, November 19th, arriving San Francisco, November 24th. All expense includes seat in plane outward, room with private shower on steamer, U. S. transportation tax, Royal Hawaiian Hotel (American Plan) $593.35

More detailed information may be found on the Transportation Information Form enclosed with the letter to Fellows, and inquiries concerning reservations may be addressed to Mr. R. R. Rickson, 179 West Jackson Boulevard, Chicago, Illinois.